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PREPARATION AND REACTIONS OF 1,2-ORTHOESTERS OF D-GLUCOPYRANOSE

BY

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled,

PREPARATION AND REACTIONS OF 1,2-ORTHOESTERS OF D-GLUCOPYRANOSE

submitted by Dirk H. Detert, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

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ABSTRACT

The initial purpose of this work was to prepare the diastereoisomeric tri-O-acetyl-1,2-O-(2'-oxacyclopentylidene)-α-D-glucopyranoses (II, IIA) and to study their usefulness in the preparation of alkyl D-glucopyranosides.

The synthesis of the spiro orthoesters was achieved by two methods: (a) from 3,4,6-tri-O-acetyl-α-D-glucopyranosyl chloride (XX) by way of tri-O-acetyl-2-O-(4'-hydroxybutyryl)-α-D-glucopyranosyl chloride (X) and reaction of this compound with tetraethylammonium chloride and 2,6-lutidine; (b) from tri-O-acetyl-1,2-O-(1'-*exo*-ethoxyethylidene)-α-D-glucopyranose (I) by reaction with 4-butyrolactone and an acid catalyst. The latter reaction was also employed to prepare a number of 1,2-O-alkylidene derivatives of D-glucopyranose. N.m.r. spectroscopy was used to determine slight differences in the conformation of the *exo* and *endo* isomers of 1,2-orthoesters of D-glucopyranose.

The reactions of 1,2-orthoesters with an alcohol and antimony pentachloride provided near quantitative yields of alkyl D-glucopyranosides. The ratio of α- to β-isomers was determined by the amount of catalyst used.

The alkyl D-glucopyranosides were obtained as their 3,4,6-tri-O-acetyl and/or tetra-O-acetyl derivatives, depending on the reaction conditions.

During the course of this work solvolysis reactions of 1,2-orthoesters of D-glucopyranose, D-galactopyranose and D-mannopyranose were studied.

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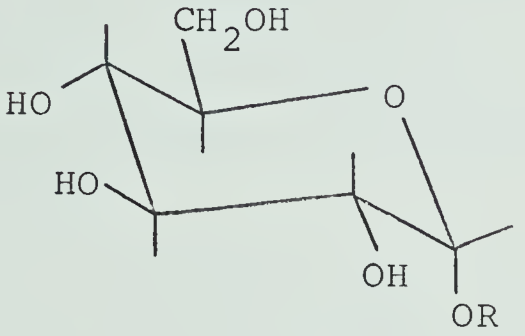
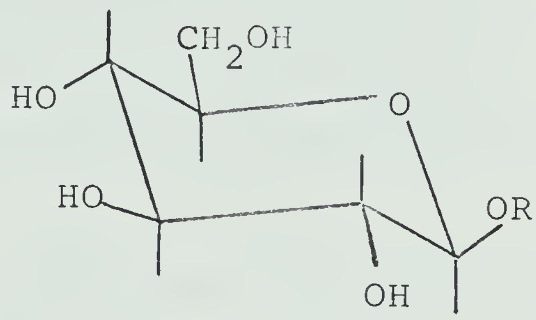
INTRODUCTION

Alkyl α- and β-D-glucopyranosides have the following configurations and conformations:



α-D-glucopyranoside



β-D-glucopyranoside

Although the conversion of D-glucose to these D-glucopyranosides merely involves the conversion of a cyclic hemiacetal to cyclic acetals, the subject has attracted much attention for nearly a hundred years. The first synthesis of a glucopyranoside was carried out by Michael (1), who condensed potassium phenoxide with tetra-O-acetyl-α-D-glucopyranosyl chloride to obtain phenyl tetra-O-acetyl-β-D-glucopyranoside. Since then many synthetic methods have been developed, but only a few have found wider application. Emil Fischer (2) reported the acid catalyzed condensation of free sugars with alcohols, a method which is restricted to the lower aliphatic

alcohols (3).

Satisfactory methods for the preparation of alkyl β-D-glucopyranosides have long been established. The Koenigs-Knorr reaction (4) is widely used in the synthesis of these compounds. Tetra-O-acetyl-α-D-glucopyranosyl halides are reacted with an alcohol, on catalysis by silver salts, to give Walden inversion at the anomeric center.

The discovery of the α-glucosidic linkage in a wide variety of naturally occurring oligosaccharides and antibiotics has stimulated attempts to synthesize α-glucopyranosides. Until recently no generally useful methods for the controlled preparation of alkyl α-D-glucopyranosides were available. The main purpose of this research was to examine certain possibilities in this regard which became apparent from the investigations by Lemieux and Morgan (5,6). These workers established a facile preparation of tri-O-acetyl-1,2-O-(1'-alkyloxyethylidene)-α-D-glucopyranoses (7) and showed that acid catalyzed alcoholysis of these orthoesters produced alkyl 3,4,6-tri-O-acetyl-α-D-glucopyranosides in good yield (8) (Diagram 1). A cyclic carbonium ion stabilized by the pyranose ring oxygen was postulated as an intermediate, thus accounting for the free hydroxyl group at C-2. Reaction of this ion with the added alcohol produced mainly

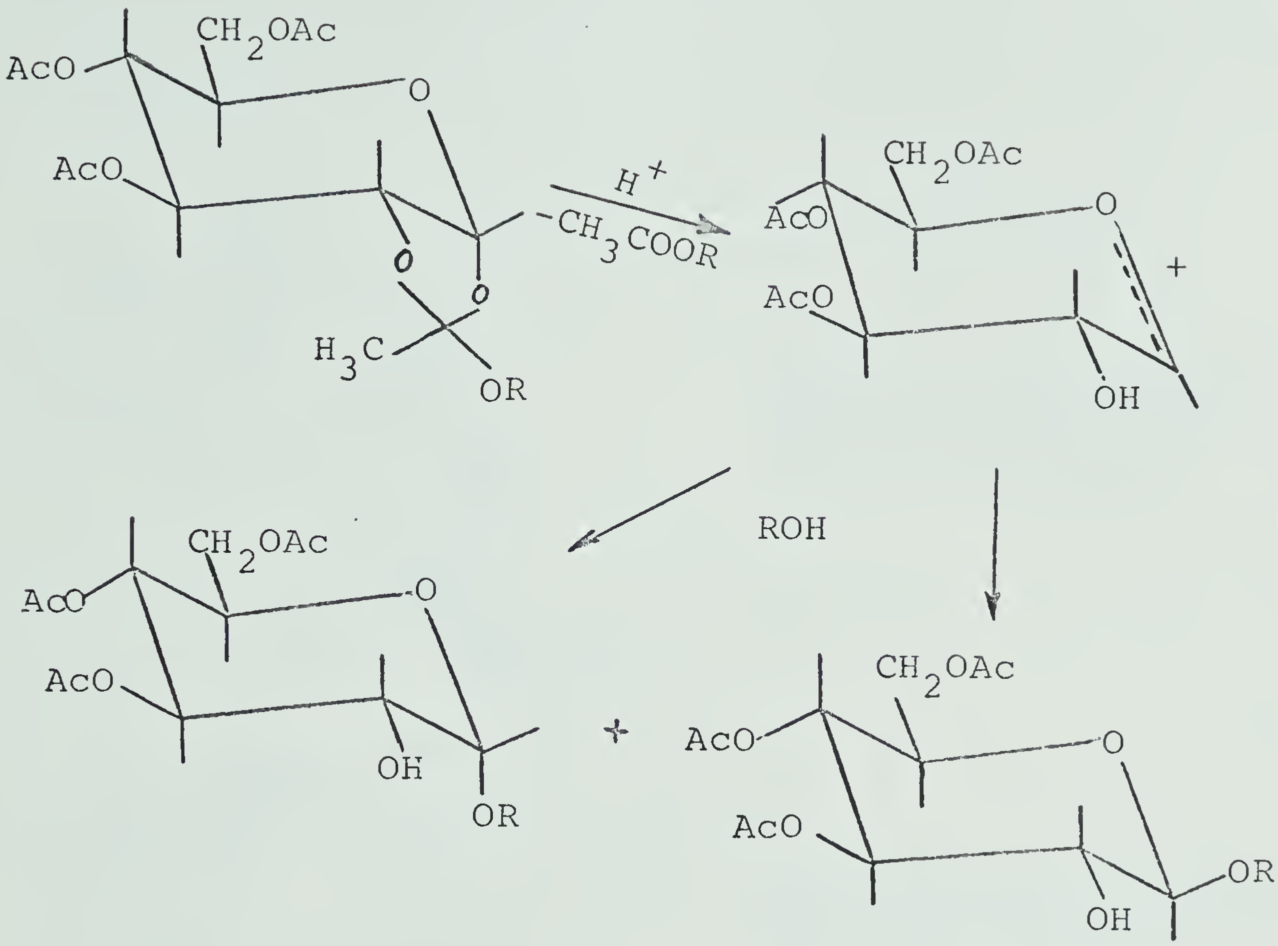


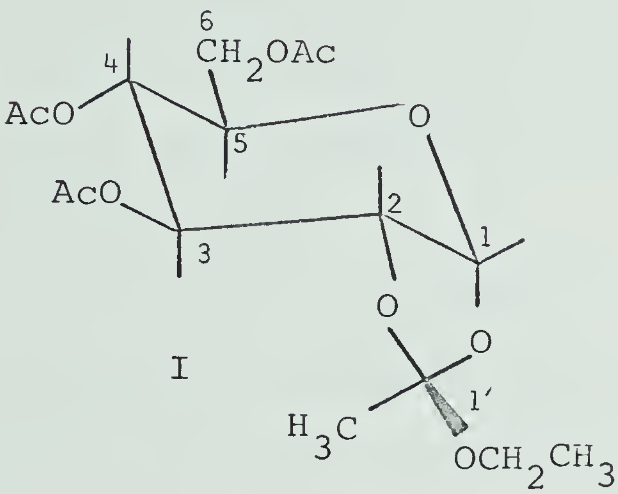
Diagram 1.

the alkyl 3,4,6-tri-O-acetyl-α-D-glucopyranoside. No appreciable yields of glucopyranosides were obtained when the alcohol was omitted.

In this research, a number of 1,2-orthoester derivatives of sugars were prepared which cannot be named following the current rules for carbohydrate nomenclature (9,10). For this reason, in this thesis, these compounds will be named as derivatives of 1,2-O-alkylidene and 1,2-O-cycloalkylidene derivatives. In so doing, the acetal carbon atom of the dioxolane ring will be designated as the

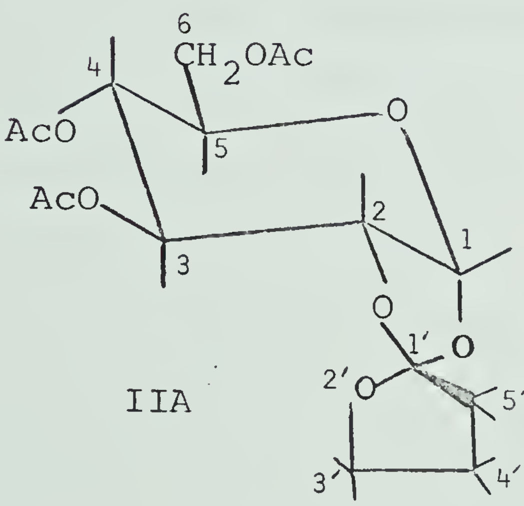
1' position. Thus, for example, two central compounds used in this research follow and are named as indicated in Diagram 2.

Diagram 2.



I

Tri-O-acetyl-1,2-O-(1'-<u>exo</u>-ethoxyethylidene)-α-D-glucopyranose.



IIA

Tri-O-acetyl-1,2-O-(2'-<u>endo</u>-oxacyclopentylidene)-α-D-glucopyranose.

The terms <u>exo</u> and <u>endo</u> are used to designate the configuration at the asymmetric carbon atom C-1' in the dioxolane ring. The isomer with the alkoxy group <u>trans</u> to the pyranose ring will be named the <u>exo</u> orthoester.

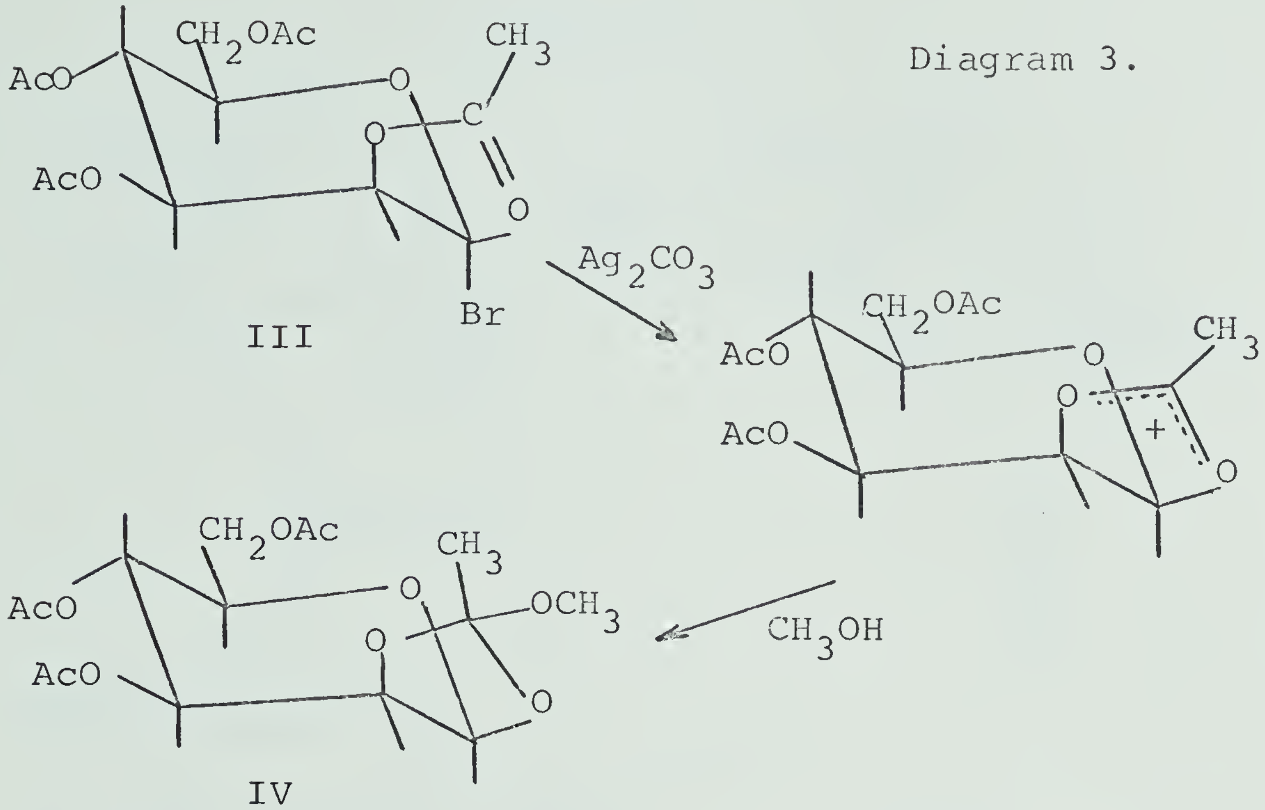
A good review of orthoesters up to 1945 has been given by E. Pacsu (11). The formation of acylated ortho-

ester derivatives was first noted in 1920 by Emil Fischer, Bergmann and Rabe (12) when an attempt was made to synthesize methyl-L-rhamnoside from 2,3,4,tri-O-acetyl-α-L-rhamnopyranosyl bromide. The structures of the so-called γ-glycosides obtained became evident through the work of both Freudenberg and Braun (13) and Bott, Haworth and Hirst (14).

It was recognized (11) that 1,2-orthoesters were obtained in reactions under Koenigs-Knorr conditions only with sugars which gave the 1,2-*trans*-acylated glycosyl halide as the thermodynamically more stable isomer. The formation of 1,2-orthoesters from these halides was attributed to participation of the 2-acyloxy group in the displacement of halogen, for example, in the case of tetra-O-acetyl-α-D-mannopyranosyl bromide (III) to form tri-O-acetyl-1,2-O-(1'-methoxyethylidene)-β-D-mannopyranose (IV) (Diagram 3).

When the highly unstable 1,2-*trans* acetylated β-D-glucopyranosyl halides became available (15,16), it was demonstrated that 1,2-orthoesters of α-D-glucopyranose could be obtained readily (15,17,18).

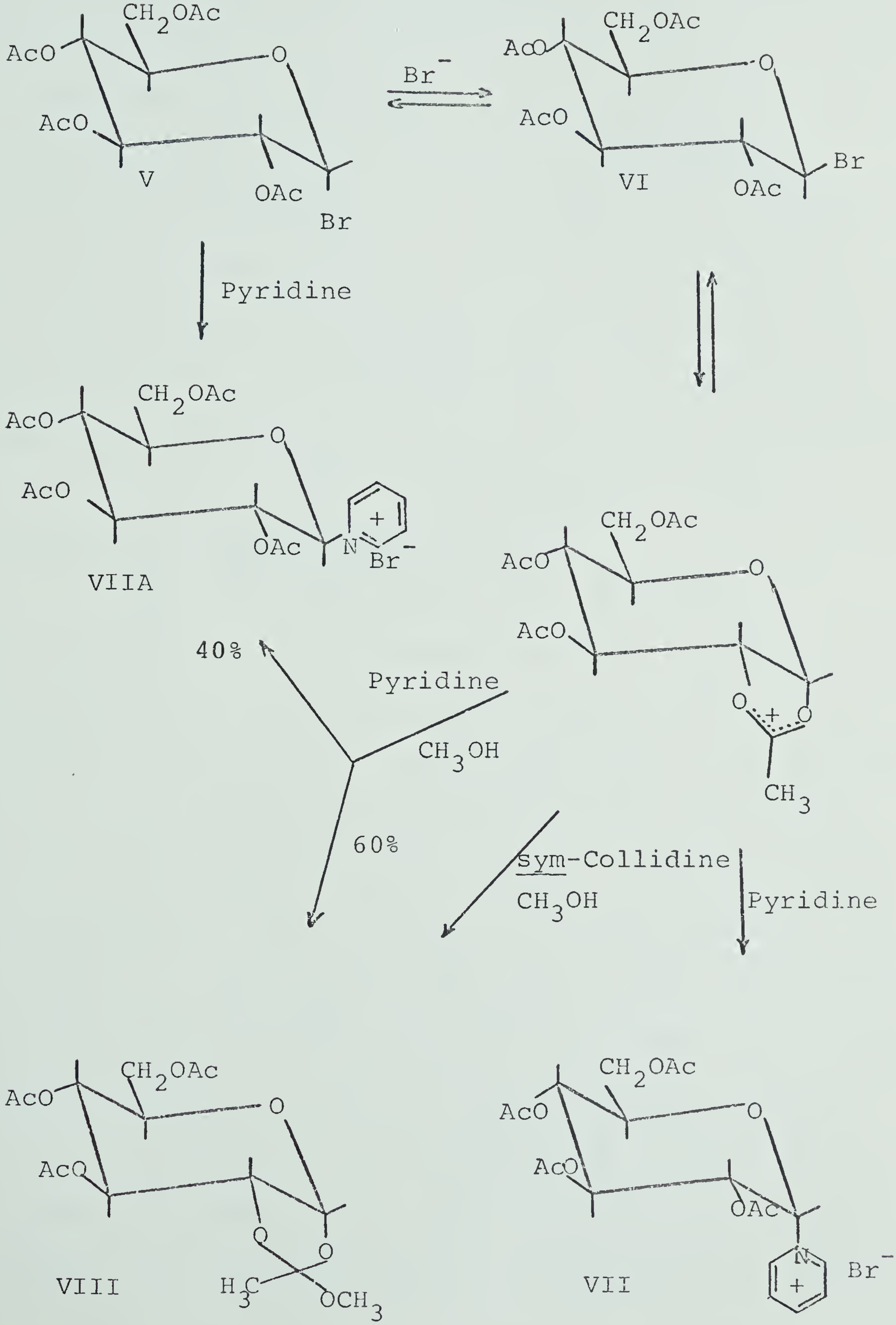
The first indication that 1,2-orthoesters of a sugar could be prepared starting from an acylated 1,2-*cis*-glucosyl halide was provided by Helferich (19,20). It was shown that the reaction of tetra-O-acetyl-α-D-



glucopyranosyl bromide (V) with 2-propanol in the presence of sym-collidine gave a product which contained over 50% of the 1,2-orthoester.

In a study of the reaction of tetra-O-acetyl-α-D-glucopyranosyl bromide (V) with pyridine (Diagram 4), Lemieux and Morgan (21) observed that bromide ion was required for the formation of N-(tetra-O-acetyl-α-D-glucopyranosyl)-pyridinium bromide (VII). When methanol was present, the α-pyridinium glucoside was not formed but, instead, tri-O-acetyl-1,2-O-(1'-methoxyethylidene)-α-D-glucopyranose (VIII) was the main product of the reaction. It was concluded, therefore, that the presence of bromide ion led to the equilibration of the α-bromide (V) with its β-anomer (VI) and that the formation of the

Diagram 4.

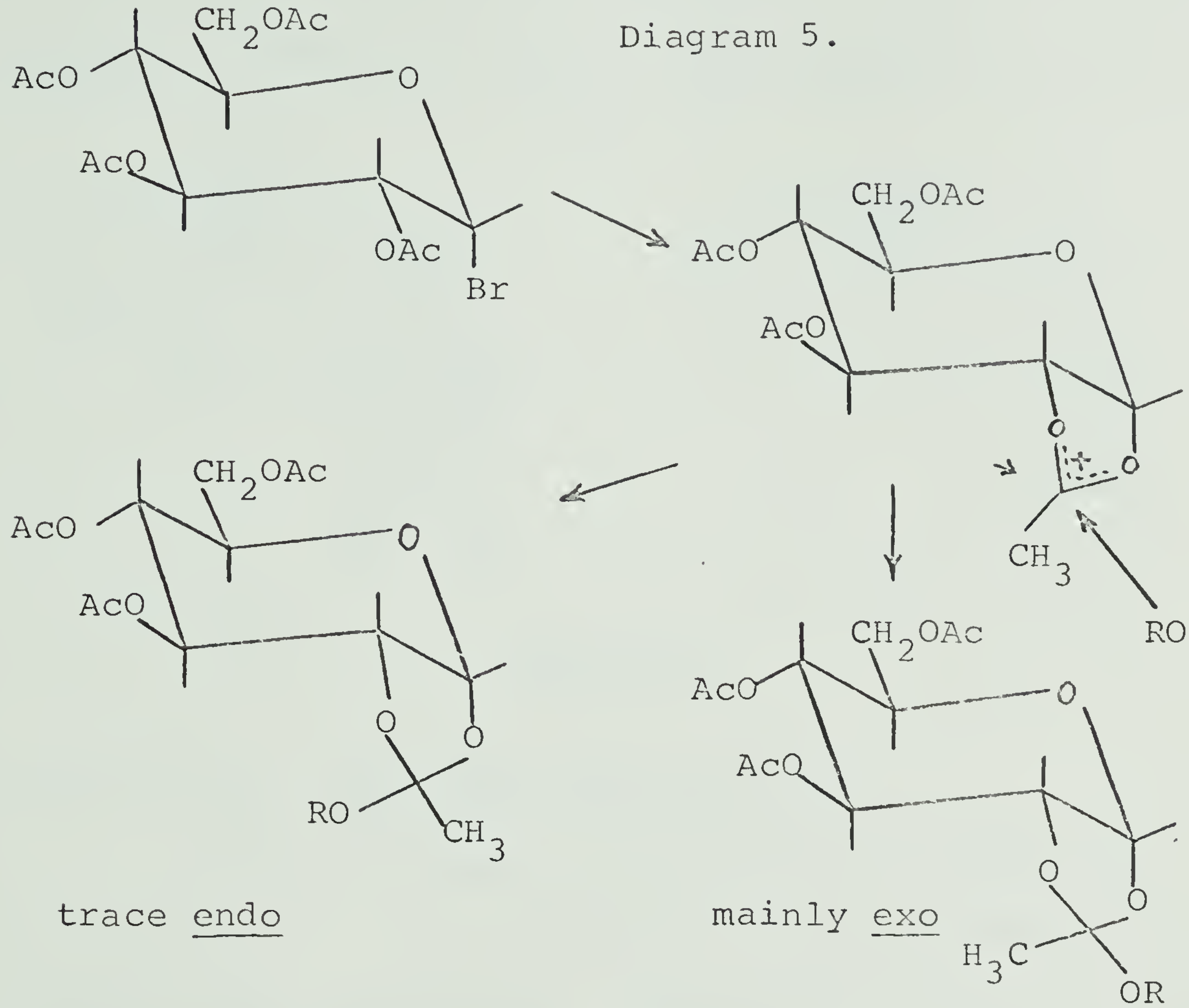


CH2OAc
AcO
AcO
V
OAc
Br
Br⁻
VI
Pyridine
VIIA
40%
60%
Pyridine
CH3OH
sym-Collidine
CH3OH
Pyridine
CH3
VIII
H3C
OCH3
VII
Br⁻

1,2-orthoester (VIII) from the β-bromide (VI) was a much faster process than the reaction of the α-bromide (V) with either pyridine or methanol or the reaction of the β-bromide (VI) with pyridine. Lemieux and Hayami (22) investigated the anomerization of tetra-O-acetyl-D-glucopyranosyl chlorides and found that these reactions are strongly catalyzed by chloride ion. From these conclusions, the generally applicable procedure for the preparation of a 1,2-orthoester from a 1,2-*cis*-glucosyl halide was developed which involved reaction of the halide with an alcohol in the presence of halide ion and a hindered base such as *sym*-collidine.

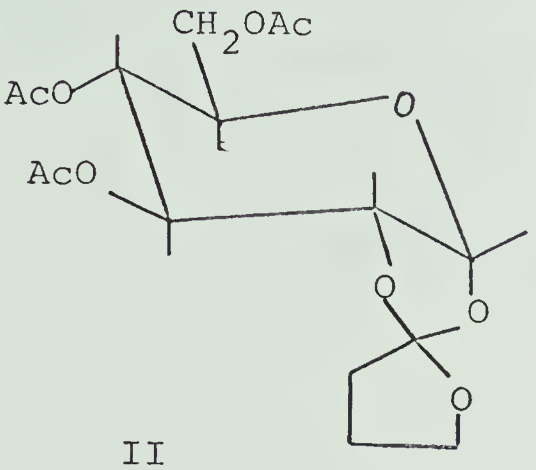
Under the indicated reaction conditions diastereoisomeric 1,2-orthoesters should be formed. But in many reactions only one isomer, usually the *exo* one, has been obtained (11). Lemieux and Cipera (18) suggested that the high degree of stereoselectivity arose because of an easier approach of the alcohol to the side of the acetoxonium ion which is *trans* to the pyranose ring (Diagram 5). Both *exo* and *endo* isomers were isolated for the first time by Talley, Reynolds and Evans (23) in the reaction of tetra-O-acetyl-α-D-glucopyranosyl bromide with 1,2,3,4-tetra-O-acetyl-β-D-glucopyranose in the presence of silver oxide. Recently Perlin (24) obtained evidence that diastereoisomeric 1,2-orthoesters of D-mannose

Diagram 5.

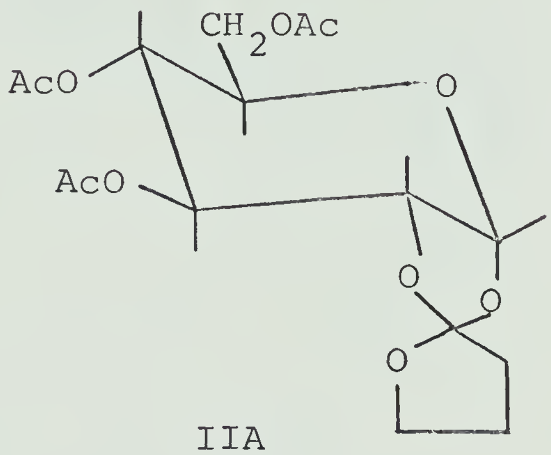


are formed under conditions of the Koenigs-Knorr synthesis when the two crystalline isomers of 1,2-O-(1'-benzyl-oxyethylidene)-β-D-mannopyranose were isolated. N.m.r. spectroscopy is well suited for the analysis of mixtures of isomeric 1,2-orthoesters and hence for the detection of small amounts of the endo isomer in the reaction products. It seems established now that both diastereoisomers are formed in all orthoester preparations (7,24, 25). In the course of this research the synthesis and separation of the two diastereoisomeric tri-O-acetyl-1,2-O-(2'-oxacyclopentylidene)-α-D-glucopyranoses (II, IIA)

was achieved (Diagram 6). These 1,2-orthoesters were prepared in order to examine their usefulness in the



II



IIA

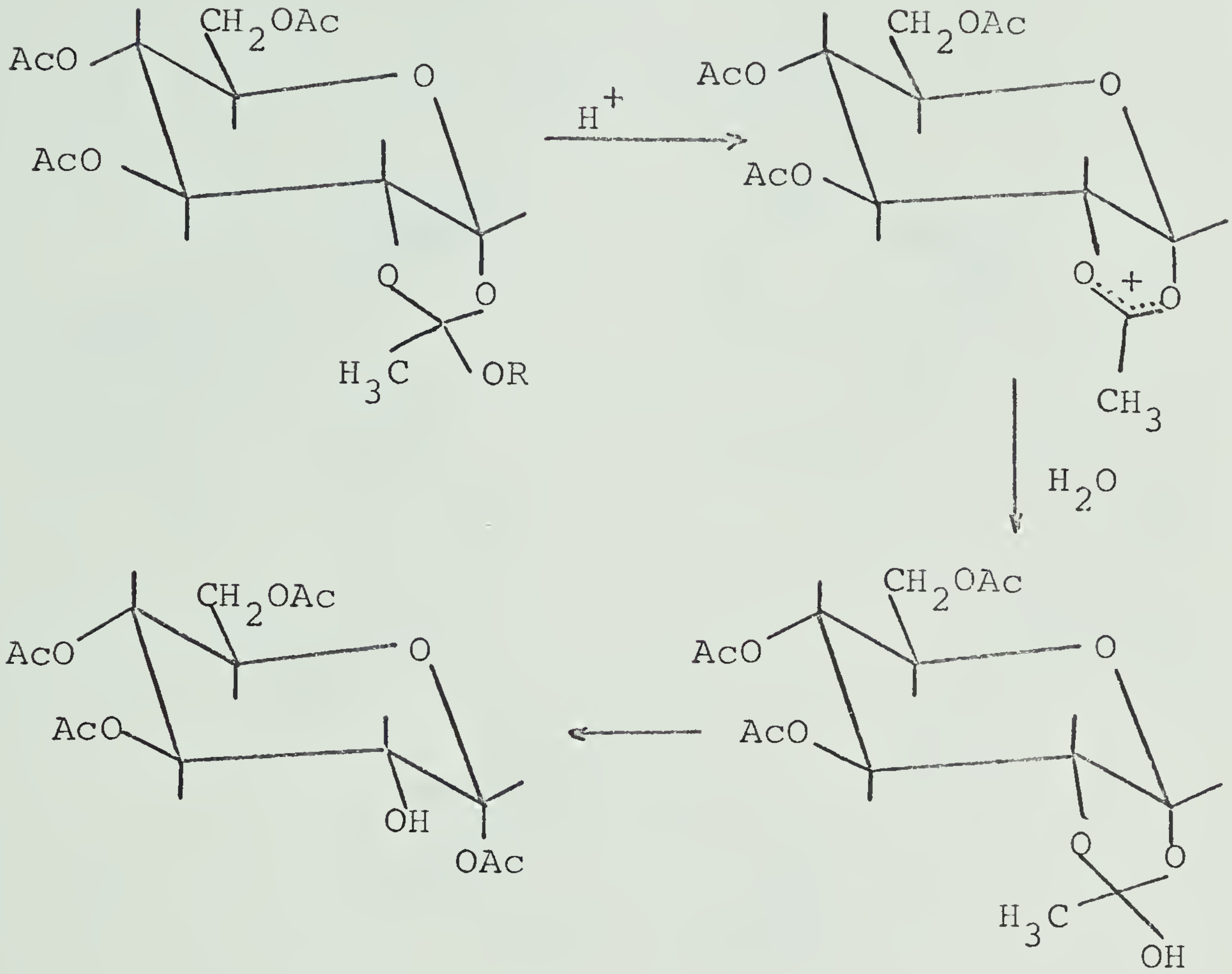
Diagram 6.

synthesis of alkyl D-glucopyranosides.

With the general availability of alkyl 1,2-orthoesters (7) the reactions of these compounds were studied more extensively. Lemieux and Cipera (18) noted the extreme sensitivity of 1,2-orthoesters toward aqueous acids. It was suggested that the 1,2-acetoxonium ion is formed very rapidly. This ion scavenges trace amounts of water to form the transient acid orthoester, which can then rearrange mainly to a product, which as we now know, is 1,3,4,6-tetra-O-acetyl-α-D-glucopyranose (IX) (Diagram 7).

In keeping with the extremely facile production of the acetoxonium ion is the observation that tri-O-acetyl-1,2-O-(1'-t-butyloxyethylidene)-α-D-glucopyranose

Diagram 7.



is converted to the corresponding isopropyloxyethylidene derivative when treated with half a mole excess of 2-propanol in methylene chloride with picric acid as the catalyst (8). Such an exchange of alkoxy groups was also observed by Ness and Fletcher (26) in the reaction of tri-O-benzoyl-2,3-O-(benzyloxybenzylidene)-β-D-fructofuranose with ethanol and a trace of acid.

The fast exchange of alkoxy groups leads to complications in the acid catalyzed alcoholysis of tri-O-acetyl-1,2-O-(1'-alkoxyethylidene)-α-D-glucopyranoses developed by Lemieux and Morgan (5,6,8) for the synthesis

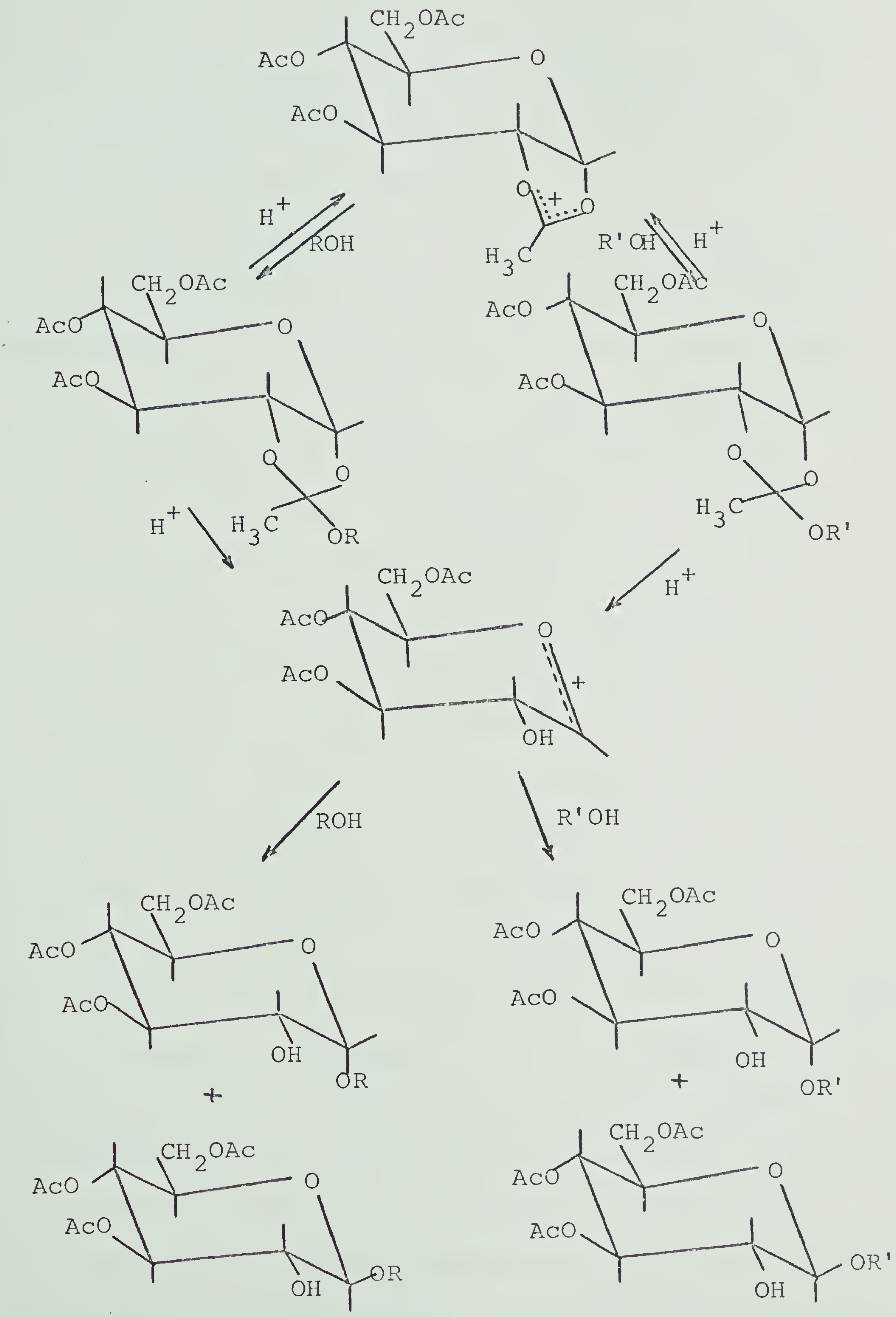


Diagram 8.

of α-glucosides. If the alkoxy group of the employed alcohol is not identical to the alkoxy group of the 1,2-orthoester, four different D-glucopyranosides are expected, as shown in Diagram 8.

In this research, we were led to expect that a spiro orthoester, e.g. tri-O-acetyl-1,2-O-(2'-oxacyclopentylidene)-α-D-glucopyranose (II, IIA), would react like an alkyl 1,2-orthoester to yield D-glucopyranosides when treated with an acid catalyst and an alcohol. However, in this case the probability of an exchange reaction might be greatly diminished (Diagram 9).

It is of interest to note that Kochetkov and co-workers (27) obtained β-D-glucopyranosides in the acid catalyzed reaction of 1,2-orthoesters with an alcohol. Tri-O-acetyl-1,2-O-(1'-ethoxyethylidene)-α-D-glucopyranose was reacted with cholesterol under various conditions with mercuric bromide and/or p-toluenesulfonic acid as the catalysts, to yield cholesteryl tetra-O-acetyl-β-D-glucopyranoside and tri-O-acetyl-1,2-O-(1'-cholesteryloxyethylidene)-α-D-glucopyranose. The formation of the acetylated β-D-glucopyranoside or the new orthoester was determined by the nature of the solvents and the type and amount of catalysts used. Helferich and Weis (20) obtained methyl tetra-O-benzoyl-β-D-glucopyranoside in the reaction of tri-O-benzoyl-1,2-O-(methoxybenzylidene)

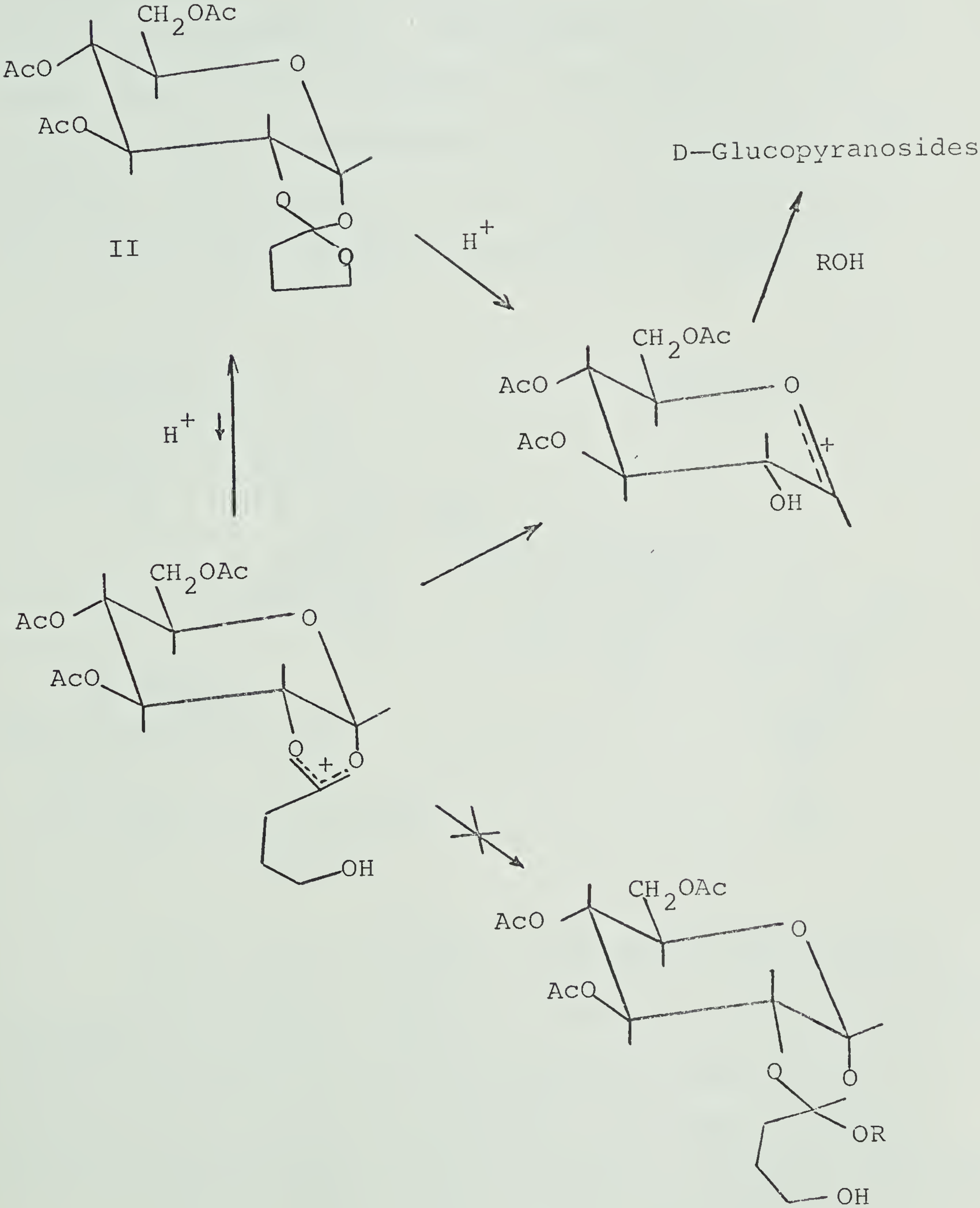


Diagram 9.

-α-D-glucopyranose with hydrogen chloride or mercuric bromide in nitromethane. The presence of methanol had little effect on the direction of the opening of the dioxolane ring. Both Kochetkov (27) and Helferich (20) explained the formation of the β-D-glucopyranoside by the rearrangement of the 1,2-orthoester (Diagram 10).

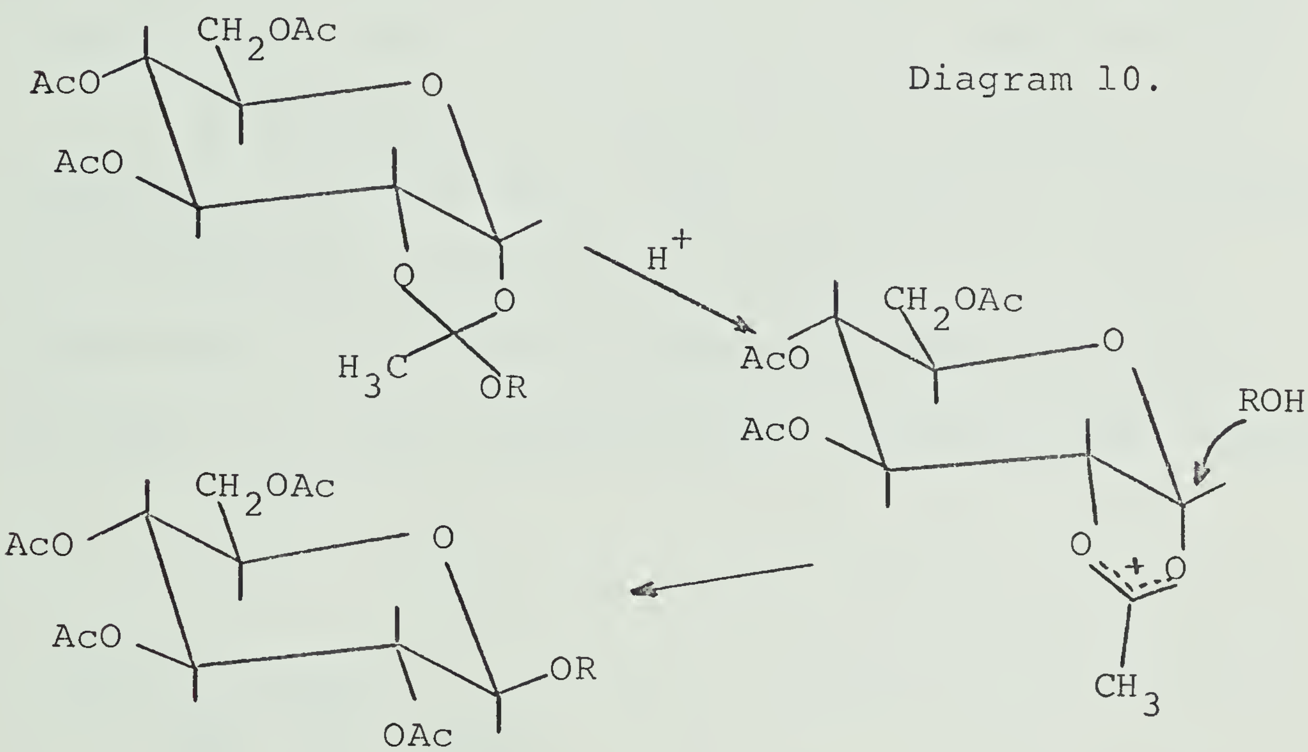


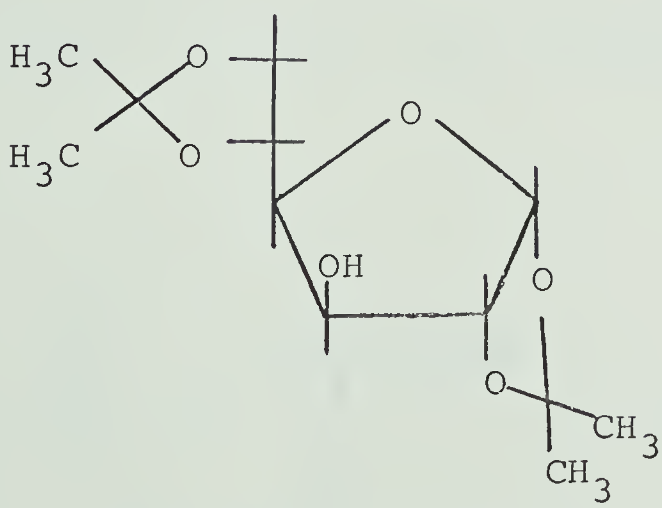
Diagram 10.

Perlin (28) obtained 3,4,6-tri-O-acetyl-D-glucopyranose and methyl 3,4,6-tri-O-acetyl-β-D-glucopyranoside, when tri-O-acetyl-1,2-O-(1'-ethoxyethylidene)-α-D-glucopyranose was treated with hydrogen chloride in methanol.

In the course of this research, a facile synthesis of 1,2-alkylidene derivatives of α-D-glucopyranose from tri-O-acetyl-1,2-O-(1'-ethoxyethylidene)-α-D-glucopyranose

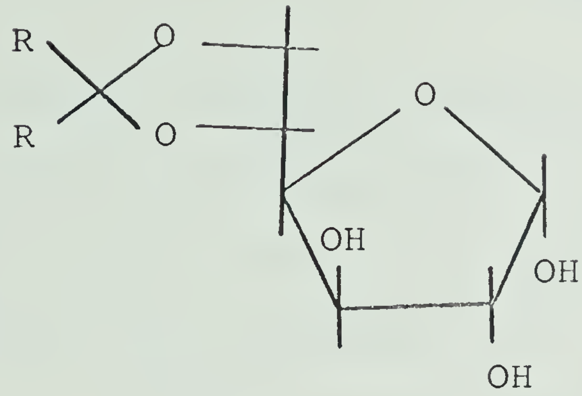
(I) was developed which may prove of general applicability for the preparation of these sugar derivatives. Cyclic ketals and acetals are among the commonest intermediates of sugar synthesis, because of their stability in alkaline solution, on one hand, and their ease of hydrolysis in acid solution on the other, and their preparation received much attention. Reviews on this subject have been given by Mills (29), Ferrier and Overend (30), and de Belder (31).

The reaction of D-glucose with aldehydes and ketones in the presence of acid catalysts was introduced into carbohydrate chemistry by Fischer (32) in the preparation of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose. All such condensations, especially with ketones,

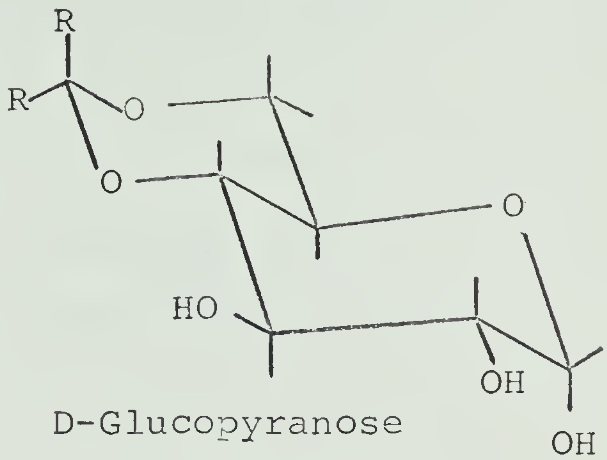


1,2:5,6-di-O-isopropylidene-α-D-glucofuranose.

tend to provide derivatives of D-glucofuranose, rather than of D-glucopyranose (33). Brown, Brewster and

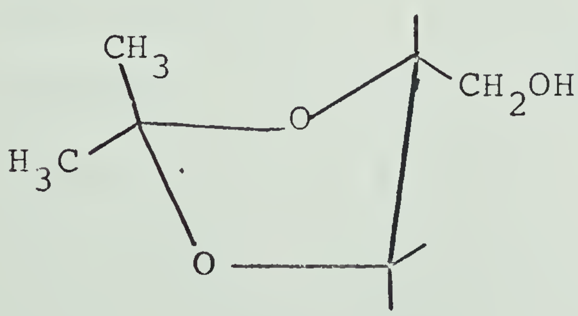


D-Glucofuranose Derivative.

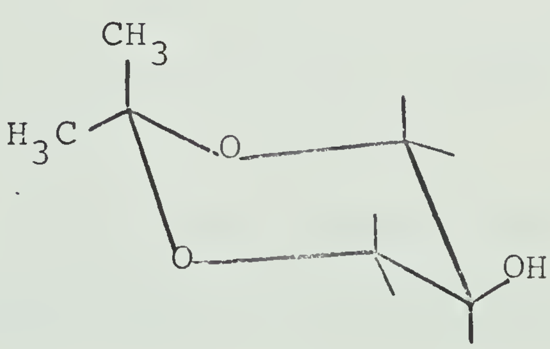


D-Glucopyranose Derivative.

Shechter (34) pointed out that the formation of a six-membered O-isopropylidene ketal is inhibited, because one methyl group is necessarily axial in the chair conformation of this six-membered ring. Hibbert and Morazain (35) showed that the reaction of glycerol with acetone leads mainly to the formation of 1,2-O-isopropylidene glycerol, rather than 1,3-O-isopropylidene glycerol. Lemieux (36) pointed out that the length of a



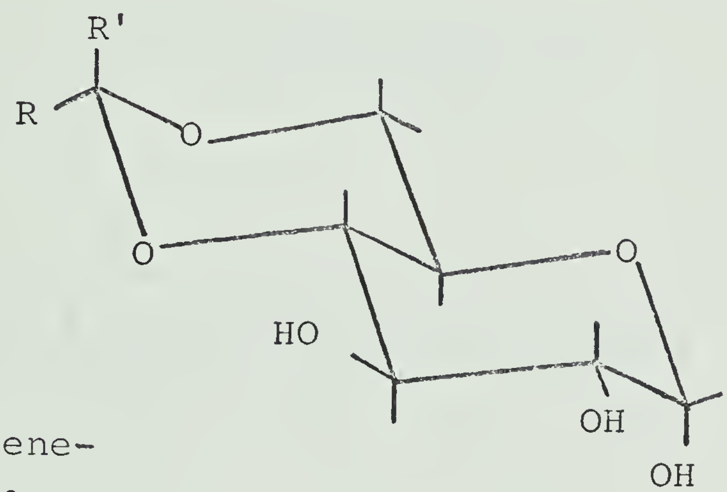
1,2-O-Isopropylidene Glycerol.



1,3-O-Isopropylidene Glycerol.

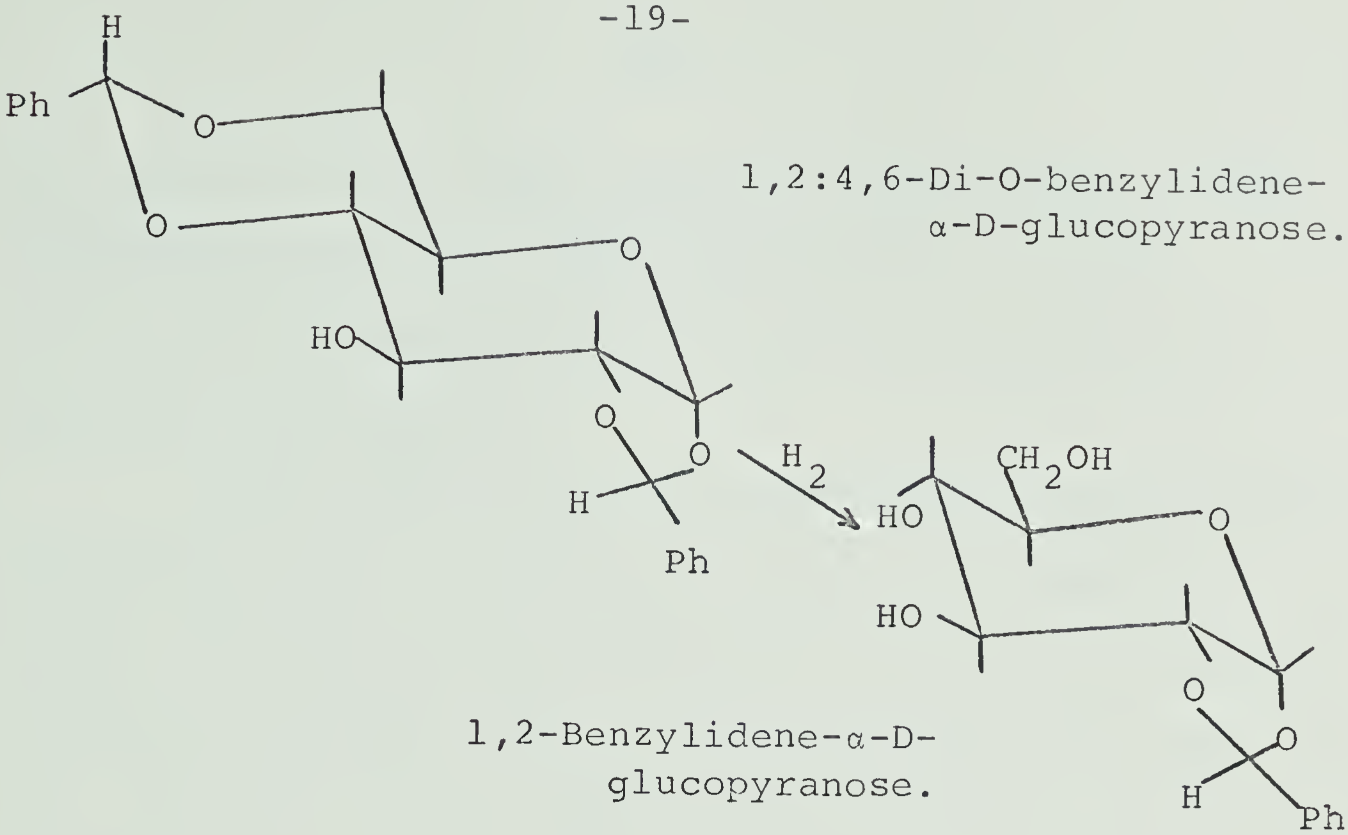
C-C bond (1.54Å) is considerably greater than that of a C-O bond (1.43Å) and that because of this reason an axial methyl group at position 2 in the 1,3-dioxane ring is even less favourable than in a cyclohexane ring.

However, with aldehydes, probably because R' in 4,6-alkylidene-D-glucopyranoses is hydrogen, such



4,6-O-alkylidene-
D-glucopyranose

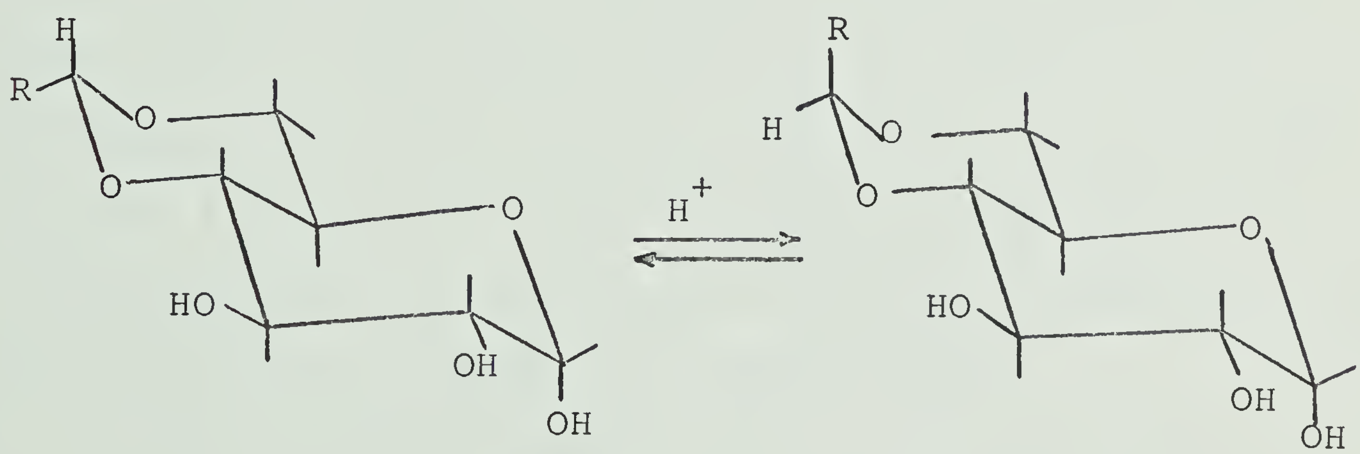
derivatives of D-glucopyranose are readily obtained, for example 4,6-O-ethylidene-D-glucopyranose (37) and 4,6-O-benzylidene-α-D-glucopyranose (38). Indeed, because of this property, in contrast to the condensation with ketones, 1,2:4,6-di-O-alkylidene derivatives of D-glucopyranose can be prepared, for example 1,2:4,6-di-O-benzylidene-α-D-glucopyranose. By partial hydrogenolysis of the latter compound 1,2-O-benzylidene-α-D-glucopyranose has been prepared (39).



1,2:4,6-Di-O-benzylidene-α-D-glucopyranose.

1,2-Benzylidene-α-D-glucopyranose.

In the acid catalyzed reaction of D-glucose with aldehydes the formation of diastereoisomers is theoretically possible. Since this reaction is reversible



(29) the products should be those of greatest thermodynamic stability. Foster and coworkers (40) determined the absolute configuration of six-membered benzylidene

derivatives on the basis of n.m.r. spectroscopy. They established that the phenyl substituent in 4,6-O-benzylidene-D-glucopyranose occupies an equatorial position, as expected.

In the preparation of five-membered cyclic acetals (derivatives of 1,3-dioxolane) there is no reason to expect the preferential formation of one diastereoisomer. Therefore various pairs of diastereoisomers are known (41), but until recently in none of the derivatives, which possess an asymmetric acetal carbon in the 1,3-dioxolane ring, is the configuration known. Rees and coworkers (42) assigned the configurations of the diastereoisomeric 1,2-O-(1'-methylpropylidene)-α-D-glucopyranoses from n.m.r. data. These workers extended a reaction developed by Hurd and Holysz (43), to the preparation of tri-O-acetyl-1,2-O-alkylidene-α-D-glucopyranoses. Hurd and Holysz (43) had obtained tri-O-acetyl-1,2-O-(1'-methylpentylidene)-α-D-glucopyranose in the reaction of tetra-O-acetyl-α-D-glucopyranosyl bromide with dibutylcadmium.

In a related reaction Coxon and Fletcher (44) prepared tri-O-acetyl-1,2-O-(1'-cyanoethylidene)-α-D-glucopyranose, besides tetra-O-acetyl-β-D-glucopyranosyl cyanide, from tetra-O-acetyl-α-D-glucopyranosyl bromide and silver cyanide in xylene.

For this research, n.m.r. spectroscopy was an essential tool for the characterization of products both as to structure and conformation (45, 46). The n.m.r. parameters of a considerable number of 1,2-orthoesters and 1,2-alkylidene derivatives of D-glucose have been published in recent years (7,62). N.m.r. studies have established that acetal rings cis-fused to pyranose rings (47) and unbridged (48,49) are non-planar.

In the present work, the calculation of dihedral angles from observed coupling constants was based on the general expression (50, 51)

$$J = x \cos^2 \theta + y.$$

The empirical parameters x and y were introduced to account for the special structural properties of cyclohexane and pyranose rings (52). Care has to be taken not to interpret the available data too strictly, since it is known that coupling constants are also subject to electronegativity and other effects (51, 53, 54). The advantage of expressing dihedral angles to the nearest degree lies in the consistency obtained within a series of compounds, rather than in the absolute magnitudes of the angles so calculated.

EXPERIMENTAL

A. Methods

I. Spectroscopic Methods.

1. Nuclear magnetic resonance (n.m.r.) spectra at 60 MHz were determined, unless otherwise stated, in deuteriochloroform with Varian A60 and A-56/60A spectrometers. N.m.r. spectra at 100 MHz were measured with a Varian H.R.100 spectrometer. Chemical shifts are reported in *tau* (τ) values relative to tetramethylsilane (TMS) used as internal standard. Double- and triple- resonance experiments were performed to confirm the assignments of signals and splittings, using a frequency sweep technique.

2. Infra-red (I.R.) spectra were obtained from chloroform solutions, with a Perkin-Elmer Grating Spectrophotometer (Model 421), unless otherwise stated. Infra-red and n.m.r. spectra were determined by Miss S. Southern, Messrs. R. N. Swindlehurst and G. Bigam, all of this Department.

II. Optical Rotations.

Optical rotations were measured with a Perkin-Elmer (Model 141) Polarimeter, or followed during reaction with a Rudolph Automatic Recording Spectropolarimeter

(Model 260/655/850/810-614). The temperature was kept constant by passing thermostated water through the jacketed tube container.

III. Melting Points.

Melting points were determined on a Leitz Microscope Heating Stage (Model 350) and, like boiling points, are uncorrected.

IV. Refractive Indices.

Refractive indices were measured with a Bausch and Lomb Constant Temperature Refractometer (Model 33-45-58).

V. Chromatographic Methods.

1. Gas-liquid chromatography (g.l.c.) was performed with an F and M Programmed Temperature Gas Chromatograph (Model 500) fitted with a thermal conductivity detector. O-Trimethylsilyl derivatives were chromatographed on a column (8' x 1/4") packed with 3% SE-30 on Chromosorb W (non acid washed,30-60 mesh). Helium was used as the carrier gas. The flow rate was approximately 100 ml/min with an inlet pressure of 30 p.s.i. The column was programmed for a temperature increase of 2.9° per minute starting from 110° and holding under isothermal

conditions at 220°.

2. Thin-layer chromatograms (t.l.c.) were run on Silica Gel G and were developed by spraying the plates with 25% sulfuric acid and heating on a hot plate. 3% Methanol in benzene was used as the developing solvent, unless otherwise stated.

3. Preparative chromatography was carried out on columns of silicic acid (100 mesh), the fractions being collected by a mechanical fraction collector. Individual fractions were examined by optical rotation and t.l.c.

VI. Elemental Analyses.

Elemental analyses were performed by Mrs. D. Mahlow of this Department.

B. Reagents

Solvents used were commercially available, and when necessary, were dried using established procedures (55). Chloroform and methylene chloride when used in preparative procedures, were purified by passing through a column of activated alumina (8).

Silica Gel G for thin layer chromatography was supplied by E. Merck, Germany. Silicic acid (100 mesh) used for preparative column chromatography was supplied by Mallinckrodt Chemical Works.

Tetraethylammonium chloride is commercially available and was dried *in vacuo* over phosphorous pentoxide. Tetra-*n*-butylammonium bromide was prepared by heating under reflux for 36 hours equimolar amounts of *n*-butyl bromide and tri-*n*-butylamine in an equal volume of acetonitrile (22). The product left on evaporation of the solvent was recrystallized from ethylacetate and dried *in vacuo* over phosphorous pentoxide.

Anhydrous *p*-toluenesulfonic acid was obtained by a method similar to that described by A. R. Morgan (8). The ether extract of the monohydrate was dried over several lots of fresh phosphorous pentoxide in succession and evaporated to a syrup *in vacuo*. The syrup was then dissolved in dry N,N-dimethylformamide and was stored sealed with a serum cap. The n.m.r. spectrum showed a signal for the acid proton at τ-6.95 with no indication of water. Samples were removed with a syringe and were titrated against standard sodium hydroxide solution just before use.

The 33% (w/w) solution of hydrogen bromide in acetic acid was prepared by passing dry hydrogen bromide gas into a flask containing dry acetic acid.

4-Butyrolactone was purified according to a procedure described in the literature (63).

Antimony pentachloride is commercially available

and was not purified prior to use.

C. The *exo* and *endo* Isomers of Tri-O-acetyl-1,2-O-(2'-oxacyclopentylidene)-α-D-glucopyranose (II, IIA).

I. From Tri-O-acetyl-2-O-(4'-hydroxybutyryl)-α-D-glucopyranosyl Chloride (X).

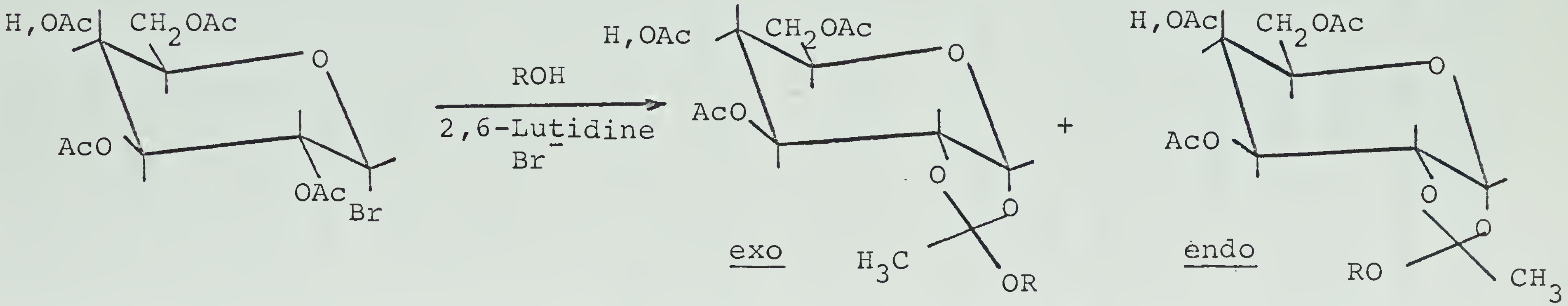
1. Tri-O-acetyl-1,2-O-(1'-*exo*-ethoxyethylidene)-α-D-glucopyranose (I).

This compound was prepared from tetra-O-acetyl-α-D-glucopyranosyl bromide (V) (56) by the method of Lemieux and Morgan (7), except that 2,6-lutidine was used instead of *sym*-collidine, since the former compound is easier to remove. 2,6-Lutidine was removed from the reaction mixture by azeotropic distillation with water *in vacuo* at 40°C, thus obviating the need to wash with hydrochloric acid. After two successive recrystallizations from ethanol and from ether the product was sufficiently pure, m.p. 97-98°, $[\alpha]_D^{25}$ + 31° (*c*, 1 in chloroform). The n.m.r. spectrum is shown in Fig. 1 and the parameters are presented in Tables I, VII.

2. Tri-O-acetyl-1,2-O-(1'-benzyloxyethylidene)-α-D-glucopyranose (XI).

This compound was prepared under conditions similar

Table I. Relative yields in the preparation of diastereoisomeric 1,2-orthoesters of sugars.



Tri-O-acetyl-1,2-O-	exo Isomer		endo-Isomer	
	Yield %	C-Me τ-value	Yield %	C-Me τ-value
(1'-n-propyloxyethylidene)-α-D-glucopyranose (XXIX).	90-95	8.29	5-10	8.45
(1'-benzyloxyethylidene)-α-D-glucopyranose (XI).	90-95	8.25	5-10	8.41
(2'-oxacyclopentylidene)-α-D-glucopyranose (II,IIA).	∿55	-	∿45	-
(1'-methoxyethylidene)-α-D-galactopyranose (XLII).	∿70	8.32	∿30	8.41
(1'-ethoxyethylidene-α-D-galactopyranose (XLIII).	∿70	8.32	∿30	8.40
(1'-benzyloxyethylidene-α-D-galactopyranose (XLIV).	90-95	8.27	5-10	8.37

to those used by Lemieux and Morgan (7). Again, 2,6-lutidine was used as the base. Since the reaction product could not be induced to crystallize, it was purified on a column of silicic acid (100 mesh) with 0.3% 2,6-lutidine and 3% methanol in benzene as the eluting solvent. The title compound was obtained in 71% yield, as a chromatographically homogeneous, colourless syrup, and had $[\alpha]_D^{25}$ + 19° (c, 2 in chloroform). The n.m.r. spectrum is shown in Fig. 2 and the parameters are presented in Tables I, VII.

Anal. calcd. for $C_{21}H_{26}O_{10}$: C, 57.5, H, 5.98%. Found: C, 57.69; H, 5.71%.

3. 1,3,4,6-Tetra-O-acetyl-α-D-glucopyranose (IX).

(a) From tri-O-acetyl-1,2-O-(1'-*exo*-ethoxyethylidene)-α-D-glucopyranose (I).

(i) Tri-O-acetyl-1,2-O-(1'-*exo*-ethoxyethylidene)-α-D-glucopyranose (I) (1.62 g, 4.3 mmoles), was dissolved in 95% aqueous acetic acid (4 ml). The reaction was followed polarimetrically and the rotation was found to reach a constant value after 10 min. The reaction mixture was freeze-dried and the volatile components were collected.

The n.m.r. spectrum of this distillate showed the presence of ethanol in aqueous acetic acid. The syrupy residue consisted of 1,3,4,6-tetra-O-acetyl-α-D-gluco-

pyranose (IX) (∿85%) and 2,3,4,6-tetra-O-acetyl-α-D-glucopyranose (XII) (∿15%), as indicated by its n.m.r. spectrum. This ratio was found by comparison of the integration values for the signals of the H-2 ring protons at τ6.12 in compound IX and at τ5.2 in compound XII. A thin layer chromatogram indicated trace amounts of a less fully acetylated compound. Addition of ether yielded 1,3,4,6-tetra-O-acetyl-α-D-glucopyranose (IX); 1.18 g (79%), m.p. 93-96. Recrystallization from ether-hexane afforded pure material, m.p. 97.5-98.5°, $[\alpha]_D^{25}$ + 143° (c, 1 in chloroform). The n.m.r. spectrum is shown in Fig. 3 and the parameters are presented in Table IV.

Anal. calcd. for $C_{14}H_{20}O_{10}$: C, 48.30; H, 5.79%. Found: C, 48.35; H, 5.65%.

In a similar experiment Lemieux and Cipera (18) used 99% aqueous acetic acid in the hydrolysis of tri-O-acetyl-1,2-O-(1'-exo-ethoxyethylidene)-α-D-glucopyranose (I) and obtained a compound with m.p. 97.5-98.7° and $[\alpha]_D^{25}$ + 122° (chloroform) which they designated as 2,3,4,6-tetra-O-acetyl-α-D-glucopyranose (XII).

(ii) Tri-O-acetyl-1,2-O-(1'-exo-ethoxyethylidene) α-D-glucopyranose (I) (2.0 g, 5.3 mmoles) was dissolved in ether (15 ml) and water (0.3 ml) was added, followed by acetic acid (0.2 ml). The reaction was followed, in this case by n.m.r. spectroscopy. The disappearance of the

orthoester H-1 signal at $\tau 4.1$ with concomitant appearance of a doublet of spacing 4Hz at $\tau 3.7$ was observed. A slow hydrolysis was noted, 80% of starting material was left after one and a half hours; after 24 hours the hydrolysis was complete and the reaction mixture contained mainly 1,3,4,6-tetra-O-acetyl-α-D-glucopyranose (IX). The solution was concentrated _in vacuo_ to a colourless syrup. Crystallization from ether-hexane afforded the title compound, 1.25 g (68%), m.p. 90-95°. Recrystallization from ether-hexane yielded pure material, m.p. 97-98°, $[\alpha]_D^{25}$ + 139° (_c_, 1 in chloroform). A mixture with the substance prepared under (i) melted at 97-98°.

Isomerization of 1,3,4,6-tetra-O-acetyl-α-D-glucopyranose (IX) in 95% aqueous acetic acid at room temperature was found to be extremely slow, as indicated by the change of the optical rotation of the solution. An n.m.r. spectrum, taken after 10 days, was found to be virtually identical to that of pure 1,3,4,6-tetra-O-acetyl-α-D-glucopyranose (IX).

Mutarotation of 2,3,4,6-tetra-O-acetyl-β-D-glucopyranose (XII A) (0.174 g, 0.5 mmole), in 95% aqueous acetic acid (5 ml) was followed polarimetrically until the rotation, $[\alpha]_D^{25}$ + 69° (_c_, 2 in chloroform), was constant (2 1/2 hours). Isomerization to 1,3,4,6-tetra-O-

acetyl-α-D-glucopyranose (IX) did not take place. An n.m.r. spectrum, taken after 10 days did not show any trace of the latter compound.

(b) From tri-O-acetyl-1,2-O-(1'-benzyloxyethylidene)-α-D-glucopyranose (XI).

(i) Palladium black (150 mg) was prehydrogenated in dry ethylacetate (10 ml) for 1 hour. Tri-O-acetyl-1,2-O-(1'-benzyloxyethylidene)-α-D-glucopyranose (XI) (875 mg, 2 mmoles), was then added and the hydrogen consumption was followed. The uptake of the theoretical amount of hydrogen (2 mmoles) was completed after 4 hours. Filtration and evaporation of the solvent under reduced pressure yielded a colourless syrup (650 mg). The n.m.r. spectrum of this product was virtually identical to that obtained from the product of hydrolysis of tri-O-acetyl-1,2-O-(1'-exo-ethoxyethylidene)-α-D-glucopyranose (I) (Exp. C.I.3. (a) (i)), representing mainly 1,3,4,6-tetra-O-acetyl-α-D-glucopyranose (IX) with a small amount of 2,3,4,6-tetra-O-acetyl-D-glucopyranose (XII). Crystallization of the syrup from ether-hexane yielded 1,3,4,6-tetra-O-acetyl-α-D-glucopyranose (IX), 430 mg (62%), mp 91-95°. Recrystallization from ether-hexane afforded pure material, m.p. 97-98°, $[\alpha]_D^{25}$ + 137° (c, 1 in chloroform), m.p. undepressed in admixture with authentic material.

(ii) When the above hydrogenolysis was carried out in the presence of a trace of 2,6-lutidine, 2,3,4,6-tetra-O-acetyl-D-glucopyranose (XII) was obtained as the main product. The n.m.r. spectrum of the syrup obtained is shown in Fig. 4. The product could not be induced to crystallize.

(iii) Hydrolysis of tri-O-acetyl-1,2-O-(1'-benzyloxyethylidene)-α-D-glucopyranose (XI) in 95% aqueous acetic acid by the method described in Exp. C.I.3.(a) (i) gave 1,3,4,6-tetra-O-acetyl-α-D-glucopyranose (IX) in 65% yield. After one recrystallization from ether-hexane a product with m.p. 96-97.5°, and $[\alpha]_D^{25}$ + 132° (c, 1 in chloroform) was obtained. The melting point was undepressed in admixture with authentic 1,3,4,6-tetra-O-acetyl-α-D-glucopyranose (IX).

4. Tetra-O-acetyl-1-O-propionyl-β-D-glucopyranose (XIII).

Tri-O-acetyl-1,2-O-(1'-exo-ethoxyethylidene)-α-D-glucopyranose (I) (1.1 g, 3 mmoles), was dissolved in dry propionic acid (5 ml) and the reaction was followed polarimetrically. The rotation reached a constant value after 30 hours. After dilution with water (15 ml) the solution was extracted twice with 10 ml amounts of chloroform. The combined extracts were washed with saturated sodium bicarbonate solution, dried over anhydrous sodium

sulfate and evaporated to a colourless syrup, which was crystallized from ethanol; 1.05 g (88%), m.p. 99-104°. One recrystallization from ethanol yielded pure material, m.p. 104-105.5°, $[\alpha]_D^{25}$ + 4° (c, 1 in chloroform). The n.m.r. spectrum is shown in Fig. 5 and the parameters are presented in Table IV. Reaction of XIII with HBr in acetic acid yielded V, m.p. 79-84°, $[\alpha]_D^{25}$ + 175° (c, 1 in chloroform), indicating that the propionyl group is located at C-1.

Anal. calcd. for $C_{17}H_{24}O_{11}$: C, 50.50; H, 5.98%; MW 404.36. Found: C, 50.35; H, 5.91%; MW 405.

Lemieux and Brice (57) reported this compound previously, m.p. 104-105°, $[\alpha]_D$ + 3.5 (c, 1.2 in chloroform).

5. 4-Benzyloxybutyric acid (XIV).

Finely cut sodium (18.0 g) was added to benzyl alcohol (108 g) in a 500 ml, three-neck, round-bottom flask equipped with a reflux condenser and a stirrer. The reaction mixture, which was protected from atmospheric moisture with a calcium chloride tube, was heated and stirred vigorously until the sodium had disappeared. 4-Butyrolactone (70 g) was then added and the mixture was stirred and heated to 160° for 12 hrs. The excess of benzyl alcohol and unreacted 4-butyrolactone were removed under reduced pressure and the residue was taken up in water (1 l.). The aqueous solution was acidified with 50% H_2SO_4 and

extracted twice with ether (300 ml). The ether layer was then dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. The residue was distilled through a column to yield 4-benzyloxybutyric acid (XIV) (64 g $\triangleq$ 41%), b.p.$_{0.5}$ = 159°, n_D^{24} = 1.5140. The n.m.r. spectrum is shown in Fig. 6 and the parameters are presented in Table V.

This compound has been reported previously by Haga (58). Saponification of 4-butyrolactone with potassium hydroxide and subsequent addition of benzyl alcohol yielded 4-benzyloxybutyric acid (XIV) , b.p.$_{10}$ 189°, n_D^{14} 1.5160. Lyle and coworkers (64) found b.p.$_{10}$ 188°, n_D 1.5098. These workers prepared 4-benzyloxybutyric acid from 3-chloropropyl benzyl ether.

(a) Attempt to isolate 4-benzyloxybutyryl chloride (XIV A).

4-Benzyloxybutyric acid (XIV) (19.4 g., 0.1 mole) in a 100 ml, two-neck, round-bottom flask equipped with a reflux condenser and a dropping funnel was dissolved in ether (10 ml) and pyridine (10 ml, 0.13 mole). Thionylchloride (7.2 g, 0.1 mole) in ether (10 ml) was added dropwise over a half-hour period while the reaction mixture was protected from atmospheric moisture with a calcium chloride tube. Subsequently the mixture was heated under reflux for two hours. The pyridinium chloride was filtered off and the solvents were removed

under reduced pressure. The residue was distilled through a column with the main fraction boiling at 35-42°/0.2 mm Hg. Gas-liquid chromatography indicated that the distillate consisted of two compounds. The n.m.r. and I.R. spectra showed the presence of 4-butyrolactone and benzyl chloride. This was confirmed by comparison of these spectra with those of an authentic mixture of these two compounds.

6. Tetra-O-acetyl-2-O-(4'-benzyloxybutyryl)-α-D-glucopyranose (XV).

(a) From 4-benzyloxybutyric acid (XIV).

1,3,4,6-Tetra-O-acetyl-α-D-glucopyranose (IX), (3.48 g, 10.0 mmoles), and dicyclohexylcarbodiimide (2.06 g, 10.0 mmoles) were dissolved in dry pyridine (15 ml). 4-Benzyloxybutyric acid (XIV) (1.94 g, 10.0 mmoles) was added and the solution kept at room temperature. White crystals were deposited immediately. After five hours, a few drops of acetic acid were added to destroy unreacted dicyclohexylcarbodiimide. The crystals (dicyclohexylurea) were removed by filtration, washed with pyridine and the pyridine solution was concentrated under reduced pressure. The resulting syrup was fractionated on a column of 120 g silicic acid with 2% methanol in benzene as the eluting solvent. A colourless syrup, 3.1 g (62%), was obtained from the fast-moving zone; this syrup crystallized when allowed to stand

and was recrystallized from ether-hexane to yield the desired product (XV), m.p. 83-84.5°, $[\alpha]_D^{25}$ + 84° (c, 1.5 in chloroform). The n.m.r. spectrum is shown in Fig. 7 and the parameters are presented in Table V. Anal. calcd. for $C_{25}H_{32}O_{12}$: C, 57.2; H, 6.16 %; MW, 524.51. Found: C, 57.0; H, 6.14%; MW, 505.

From a slower moving zone a compound, (1.1 g) was isolated, the n.m.r. spectrum of which showed strong absorption bands at τ8-9 and also the characteristic features of the 4-benzyloxybutyryl group, but no indications of the ring protons of a glucopyranose ring.

(b) From 4-benzyloxybutyryl chloride (XIVA).

4-Benzyloxybutyric acid (XIV) (1.94 g, 10.0 mmoles), was dissolved in dry ether (10 ml) containing dry pyridine (0.8 g, 10.5 mmoles). Thionyl chloride (1.18 g, 10.0 mmoles), was then added dropwise during a half hour period, while the reaction mixture was protected from atmospheric moisture with a calcium chloride tube. A white precipitate appeared immediately. After a further 1/2 hour a solution of 1,3,4,6-tetra-O-acetyl-α-D-glucopyranose, (IX) (3.48 g, 10.0 mmoles) in dry ether (20 ml) containing dry pyridine (0.8 ml, 10.5 mmoles) was added over 1/2 hour. The mixture was stirred and kept for 1 hour at room temperature, ether (60 ml) was added and the solution was poured into

100 ml of water (near 0°) contained in a separatory funnel. The ether layer was then washed with a saturated aqueous sodium bicarbonate solution (50 ml) and dried over anhydrous sodium sulfate. Filtration and concentration of the ether solution yielded a yellow syrup, which was dissolved in ether-hexane. Seeding, with crystals obtained in the previous experiment, afforded crystalline product, 3.3 g (65%). Recrystallization from ether-hexane yielded pure material, m.p. 83-84.5°, $[\alpha]_D^{25}$ + 83° (c, 1.5 in chloroform). A mixture with the substance prepared in the previous experiment melted at 83-84.5°. The n.m.r. and I.R. spectra of these two substances were identical.

7. Tetra-O-acetyl-2-O-(4'-hydroxybutyryl)-α-D-glucopyranose (XVI).

Palladium black (0.25 g) was prehydrogenated in absolute methanol (8 ml) at room temperature and atmospheric pressure for 1 hour. Tetra-O-acetyl-2-O-(4'-benzyloxybutyryl)-α-D-glucopyranose (XV) (2.63 g, 5 mmoles), was then added and the hydrogen consumption was followed. The uptake of the theoretical amount of hydrogen (5 mmoles) was completed after one and a half hours. Filtration and evaporation of the solvent under reduced pressure yielded a colourless syrup, 2.05 g (94%), $[\alpha]_D^{25}$ + 82° (c, 1 in chloroform) which resisted crystallization. Thin layer

chromatography showed the presence of only one spot. The n.m.r. spectrum is shown in Fig. 8 and the parameters are presented in Table V.

Anal. calcd. for $C_{18}H_{26}O_{12}$: C, 49.80; H, 5.97%; MW, 438.39. Found: C, 50.39; H, 5.80%; MW, 443.

8. Reactions of penta-O-acyl-α-D-glucopyranoses with hydrogen bromide in acetic acid.

(a) Penta-O-acetyl-α-D-glucopyranose (XVII).

This compound was prepared, following the directions given by Wolfrom and Thompson (59). The compound melted at 112-113° and had $[\alpha]_D^{25}$ + 105° (*c*, 1 in chloroform).

The results of a series of rate studies in the formation of tetra-O-acetyl-α-D-glucopyranosyl bromide (V) under various conditions are shown in Table II and Figs. 9 and 10. All reactions were followed polarimetrically using a Rudolph recording polarimeter operating at the sodium D-line (589 mμ), until maximum rotation was attained. In a typical experiment penta-O-acetyl-α-D-glucopyranose (XVII) (59,60) (0.390 g, 1.0 mmole) was dissolved at zero time in a 33% (w/w) solution of hydrogen bromide in acetic acid (10 ml). The solution was rapidly transferred to a polarimeter tube maintained at 25° by the circulation of thermostated water. The change in rotation

Table II. Rate studies in the formation of tetra-O-acetyl-α-D-glucopyranosyl bromide (V) from penta-O-acetyl-D-glucopyranoses.

Pentaacetate 0.1 mmole	HBr/solvent ml	Co-solvent ml	HBr/solution %(w/v)	Time min.
XVII	10 HOAc	-	47	<4
"	5 "	5 Ac_2O	-	-
"	6.7 "	3.3 HOAc	31.5	15
"	5 "	5 "	23.5	30
"	3.3 "	6.7 "	15.5	70
"	2 "	8 "	9.4	130
"	1 "	9 "	4.7	450
" [a]	1 "	9 "	4.7	450
"	0.7 "	9.3 "	3.3	1100
"	2 "	8 $CHCl_3$	4.7	160
"	2 "	8 C_6H_6	4.7	300
"	10 $CHCl_3$	-	0.33	> 3 days
XVIIA	10 HOAc	-	47	<4
"	6.7 "	3.3 HOAc	31.5	10
"	5 "	5 "	23.5	15
"	3.3 "	6.7 "	15.5	30
"	2 "	8 "	9.4	50
"	1 "	9 "	4.7	120
" [a]	1 "	9 "	4.7	120

a. Tetra-n-butylammonium bromide (6 mmoles) added.

with reaction time was provided by the chart record. After the rotation reached a constant value $CHCl_3$ (20 ml) was added and the mixture was washed with ice water (20 ml) and a saturated $NaHCO_3$ solution (10 ml). The $CHCl_3$ solution was then stirred for a few minutes with anhydrous sodium sulfate and taken to dryness under reduced pressure. After the resulting syrup was dissolved in ether, crystallization occurred immediately to yield tetra-O-acetyl-α-D-glucopyranosyl bromide (V), 0.34 g (82%), m.p. 86-88°, $[\alpha]_D^{25}$ + 190° (c, 2 in chloroform), undepressed in admixture with authentic material. The n.m.r. spectrum of the crude reaction product showed quantitative conversion of the pentaacetate (XVII) to the bromide (V) judged by the disappearance of the signal for the anomeric proton of XVII at τ3.65 and the presence of the signal for the anomeric proton of V at τ3.40.

(b) Tetra-O-acetyl-2-O-(4'-hydroxybutyryl)-α-D-glucopyranose (XVI).

(i) This compound (0.870 g, 2.0 mmoles), was dissolved in a cold 33% (w/w) solution of hydrogen bromide in acetic acid (2 ml). The mixture was kept at 0° C for 30 minutes. Then chloroform (10 ml) was added and the mixture was washed with ice-water (10 ml) and a cold saturated sodium bicarbonate solution (10 ml). The

chloroform solution was then stirred with anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Crystallization from ether-hexane afforded tetra-O-acetyl-α-D-glucopyranosyl bromide (V), 0.51 g (62%), m.p. 78-83°, $[\alpha]_D^{25}$ + 176° (c, 1 in chloroform). The n.m.r. spectrum of the crude reaction product indicated the presence of ∿85% tetra-O-acetyl-α-D-glucopyranosyl bromide (V) and of ∿15% 3,4,6-tri-O-acetyl-α-D-glucopyranosyl bromide (XVIII), judged by the comparison of the integrations for the signals of the anomeric protons at τ3.40 and τ3.45 respectively. 4-Butyrolactone was detected in the n.m.r. spectrum by absorption bands centered at τ5.7 and τ7.6.

In an identical experiment the syrup obtained was subjected to high vacuum distillation and the volatile products were collected. A chloroform solution of these products was analyzed by g.l.c. The peaks coincided with those of an authentic sample of 4-butyrolactone in chloroform.

(ii) In an additional experiment the reaction time was shortened to 10 minutes. After the workup, indicated above, the syrup obtained was examined by n.m.r. The spectrum showed the presence of ∿35% tetra-O-acetyl-α-D-glucopyranosyl bromide (V) and ∿65% 3,4,6-tri-O-acetyl-α-D-glucopyranosyl bromide (XVIII), as well as 4-butyro-

lactone.

(iii) When tetra-O-acetyl-2-O-(4'-hydroxybutyryl)-α-D-glucopyranose (XVI) was reacted with a 22% (w/w) solution of hydrobromic acid in propionic acid for 30 minutes at 0°C, the main reaction product was found to be 3,4,6-tri-O-acetyl-2-O-propionyl-α-D-glucopyranosyl bromide (XIX). The n.m.r. spectrum is shown in Fig. 11 and the parameters are presented in Table IV.

(iv) Reaction of tetra-O-acetyl-2-O-(4'-benzyloxybutyryl)-α-D-glucopyranose (XV) with a 33% (w/w) solution of hydrogen bromide in acetic acid under the conditions described above (i) gave the same products as in (i), judged from the n.m.r. spectrum.

9. 3,4,6-Tri-O-acetyl-α-D-glucopyranosyl chloride (XX).

This compound was prepared from 3,4,6-tri-O-acetyl-β-D-glucopyranosyl chloride (61) by the procedure of Lemieux and Hayami (22). Three recrystallizations from ether-hexane gave the pure product, m.p. 93-94°, $[\alpha]_D^{25}$ + 148° (c, 2 in chloroform). The n.m.r. spectrum is shown in Fig. 12 and the parameters are presented in Table V.

10. Tri-O-acetyl-2-O-(4'-benzyloxybutyryl)-α-D-glucopyranosyl chloride (XXI).

(a) From 4-benzyloxybutyric acid (XIV).

3,4,6-Tri-O-acetyl-α-D-glucopyranosyl chloride (XX)

(3.25 g, 10.0 mmoles), and dicyclohexylcarbodiimide (2.06 g, 10.0 mmoles), were dissolved in dry pyridine (15 ml). 4-Benzyloxybutyric acid (XIV) (1.94 g, 10.0 mmoles), was added and the solution was kept at room temperature for five hours. Using the standard work-up (Exp. C.I. 6. (a)), a colourless syrup, 3.2 g (64%) was obtained after column chromatography. The product was found to be chromatographically homogeneous and had an optical rotation of $[\alpha]_D^{25}$ + 133° (c, 1 in chloroform). The n.m.r. spectrum is shown in Fig. 13 and the parameters are presented in Table V.

Anal. calcd. for $C_{23}H_{29}O_{10}Cl$: C, 55.2; H, 5.97; Cl, 7.08%. Found: C, 55.19; H, 6.05; Cl, 7.20%.

(b) From 4-benzyloxybutyryl chloride (XIVA).

4-Benzyloxybutyric acid (XIV) (1.94 g, 10.0 mmoles), was dissolved in ether (10 ml) containing dry pyridine (0.8 g, 10.5 mmoles). Thionyl chloride (1.10 g, 10.0 mmoles), was then added during a half-hour period, while the reaction mixture was protected from atmospheric moisture with a calcium chloride tube. A yellow precipitate appeared immediately. After a further 1/2 hour a solution of 3,4,6-tri-O-acetyl-α-D-glucopyranosyl chloride (XX), (3.25 g, 10.0 mmoles), in ether (20 ml) containing dry pyridine (0.8 g, 10.5 mmoles) was added

over 1/2 hour. The mixture was stirred and kept for one hour at room temperature, washed with water, saturated sodium bicarbonate solution and dried over sodium sulfate. After filtration the solution was concentrated to a yellow-brown syrup. Subsequent fractionation on a column of silicic acid (140 g) with 3% methanol in benzene as the eluting solvent yielded a colourless syrup, 2.95 g (59%), $[\alpha]_D^{25}$ + 140° (c, 1 in chloroform). The n.m.r. spectrum of this product was identical to the one obtained from the material prepared in the previous experiment.

11. Tri-O-acetyl-2-O-(4'-hydroxybutyryl)-α-D-glucopyranosyl chloride (X).

Palladium black (0.15 g), was prehydrogenated in absolute methanol (10 ml), at room temperature and atmospheric pressure for one hour. Tri-O-acetyl-2-O-(4'-benzyloxybutyryl)-α-D-glucopyranosyl chloride (XXI) (2.5 g, 5 mmoles), was then added and the hydrogen consumption was followed. The uptake of the theoretical amount of hydrogen (5 mmoles) was completed after 3/4 hour. Filtration and evaporation of the solvent under reduced pressure yielded a colourless syrup, 1.95 g (95%), which resisted crystallization. T.l.c. showed the presence of only one spot. The n.m.r. spectrum is shown in Fig. 14 and the parameters are presented in Table V. The optical

rotation was found to be $[\alpha]_D^{25}$ + 122° (c, 1 in chloroform).

12. Tri-O-acetyl-1,2-O-(1'-methoxy-4'-benzyloxybutylidene)-α-D-glucopyranose (XXII).

Tri-O-acetyl-2-O-(4'-benzyloxybutyryl)-α-D-glucopyranosyl chloride (XXI) (0.5 g, 1 mmole), was dissolved in 2,6-lutidine (1 ml), methylene chloride (1 ml) and dry methanol (1 ml). Tetraethylammonium chloride (0.1 g, 0.75 mmole), was added and the mixture kept at 50° for 24 hours. Chloroform (10 ml) was added and the solution was washed with cold water (2 x 10 ml). Removal of the solvents by azeotropic distillation with water under reduced pressure yielded a syrup, which could not be induced to crystallize. The n.m.r. spectrum is shown in Fig. 15 and the parameters are presented in Table V.

13. Formation of the title compounds (II, IIA).

Tri-O-acetyl-2-O-(4'-hydroxybutyryl)-α-D-glucopyranosyl chloride (X) (2.05 g, 5 mmoles), was dissolved in 2,6-lutidine (4 ml) and acetonitrile (3 ml). Tetraethylammonium chloride (0.5 g, 3 mmoles), was added, and on warming to 45°C a homogeneous solution was obtained. 2,6-Lutidinium chloride soon began to form. After 24 hours at 45° the reaction mixture was dissolved in chloroform (20 ml) and washed with cold water (2 x 20 ml). Removal of the solvents by azeotropic distillation with

water yielded a yellow syrup, which was fractionated on a column of silicic acid (80 g) with 0.3% 2,6-lutidine and 3% methanol in benzene as the eluting solvent. Fractions of 10 ml of eluate were collected. From the fast moving zone a syrup was obtained, 1.25 g (67%), which crystallized after a few hours. Thin-layer chromatography showed the presence of only one spot. N.m.r. spectroscopy indicated that the two diastereo-isomeric orthoesters had formed with the endo isomer predominating slightly, judged by the integrations for the signals of the anomeric protons. The n.m.r. spectrum of the mixture is shown in Fig. 16. The assignment of the signals could be verified by nuclear magnetic double resonance experiments. Repeated recrystallizations from ether-hexane yielded the pure endo-1,2-orthoester (IIA), m.p. 116-117°, $[\alpha]_D^{25}$ + 85° (c, 1 in chloroform). The exo-1,2-orthoester (II) was recovered from the mother liquors as a virtually pure syrup, $[\alpha]_D^{25}$ + 42° (c, 1 in chloroform). The n.m.r. spectra of the separated isomers II and IIA are shown in Figs. 17 and 18 respectively and the parameters are presented in Table VII. Anal. calcd. for $C_{16}H_{22}O_{10}$: C, 51.25; H, 5.89%. Found: crystalline IIA (endo): C, 51.06; H, 5.79%; syrupy II (exo): C, 51.38; H, 6.06%.

In another experiment, after the fractionation on

a silicic acid column, fractions of the fast moving zone were evaporated separately and examined by n.m.r. Fractions 35-37 yielded virtually pure endo isomer (IIA) and fractions 47-49 gave pure exo orthoester (II), fractions 38-46 contained a mixture of both compounds.

II. Preparation of the Epimeric Tri-O-acetyl-1,2-O-(2'-oxacyclopentylidene)-α-D-glucopyranoses (II, IIA) from Tri-O-acetyl-1,2-O-(1'-exo-ethoxyethylidene)-α-D-glucopyranose (I).

1. Formation of the diastereoisomers of tri-O-acetyl-1,2-O-(1'-ethoxyethylidene)-α-D-glucopyranose (I, IA).

Pure tri-O-acetyl-1,2-O-(1'-exo-ethoxyethylidene)-α-D-glucopyranose (I) (0.375 g, 1 mmole), was dissolved in dry 4-butyrolactone (1 ml) in a flask sealed with a serum cap. After the addition of dry p-toluenesulfonic acid in N,N-dimethylformamide, (0.05 ml, 0.08 mmole by titration), the solution was kept at room temperature for five hours. 2,6-Lutidine (0.1 ml) and chloroform (10 ml) were added and the solution was washed with water (10 ml) and a saturated aqueous sodium bicarbonate solution (10 ml). The syrup, obtained on evaporation, was fractionated on a column of silicic acid (40 g) with 3% methanol, 0.3% 2,6-lutidine in benzene as the eluting

solvent. From the fast-moving zone a syrup was obtained; the n.m.r. spectrum of this (Fig. 19) showed that the diastereoisomeric tri-O-acetyl-1,2-O-(1'-ethoxyethylidene)-α-D-glucopyranoses (I, IA) had been recovered. From the integration values of the signals for the C-methyl protons at τ8.28 and τ8.43 it was estimated that the mixture consisted of the exo isomer (I) (65-70%) and the endo compound (IA) (30-35%). The syrup crystallized on standing. After two recrystallizations from ethanol the substance melted at 96-97.5°, $[\alpha]_D^{25}$ + 33° (*c*, 1 in chloroform), indicating pure tri-O-acetyl-1,2-O-(1'-*exo*-ethoxyethylidine)-α-D-glucopyranose (I). This was confirmed by a mixed melting point (96-97°C) with authentic material and a direct comparison of n.m.r. spectra.

2. Formation of the title compounds (II, IIA).

Tri-O-acetyl-1,2-O-(1'-*exo*-ethoxyethylidene)-α-D-glucopyranose (I) (3.75 g, 10.0 mmoles) was dissolved in dry 4-butyrolactone (7 ml) in a flask sealed with a serum cap. A solution of dry *p*-toluenesulfonic acid in N,N-dimethylformamide (3 ml, 5.0 mmoles by titration), was added and the mixture was left at room temperature for 24 hours. 2,6-Lutidine (2 ml) and chloroform (20 ml) were added and the solution was washed with water (20 ml)

and a saturated aqueous sodium bicarbonate solution (10 ml). After drying the chloroform solution by filtration through chloroform-wetted filter paper the solvents were evaporated under reduced pressure. The syrup obtained was fractionated on a column as described above (Exp. C.I. 13) to yield a mixture of the diastereoisomeric orthoesters (II, IIA), 2.1 g (56%). From the n.m.r. spectrum it was estimated that in this case the _exo_-isomer (II) predominated slightly. The syrup was dissolved in ether-hexane and the solution was seeded with tri-O-acetyl-1,2-O-(2'-_endo_-oxacyclopentylidene)-α-D-glucopyranose (IIA), obtained from Exp. C.I. 13. Repeated recrystallizations of the crystals obtained yielded a compound, m.p. 115.5-117°, $[\alpha]_D^{25}$ + 81° (_c_, 1 in chloroform), which in admixture with the material obtained in C.I. 13. did not show a melting point depression, indicating the formation of tri-O-acetyl-1,2-O-(2'-_endo_-oxacyclopentylidene)-α-D-glucopyranose (IIA). The _exo_ isomer (II) was obtained as a syrup, $[\alpha]_D^{25}$ + 47° (_c_, 1 in chloroform), either by a chromatographic isolation (Exp. C.I. 13) from the crude reaction mixture or from the mother liquors of the above recrystallization procedure.

D. Formation of Alkyl D-Glucopyranosides from Tri-O-acetyl-1,2-O-(1'-alkoxyalkylidene)-α-D-glucopyranoses.

Reaction of tri-O-acetyl-1,2-O-(1'-alkyloxyalkylidene)-α-D-glucopyranoses with an alcohol in the presence of an acid catalyst yielded anomeric alkyl tri-O-acetyl-D-glucopyranosides, alkyl tetra-O-acetyl-D-glucopyranosides and products which could be deacetylated to give α- and β-D-glucose. The mixtures obtained were analyzed by one or more of the following methods: g.l.c., t.l.c., n.m.r., preparative column chromatography. In the case of g.l.c. analysis we followed the procedure used by Morgan (8).

In preliminary experiments known mixtures of α- and β-alkyl tetra-O-acetyl-D-glucopyranosides, α- and β-penta-O-acetyl-D-glucopyranose and tetra-O-acetyl-pentaerythritol (used as internal standard) were de-acetylated with triethylamine in methanol-water, converted to their trimethylsilyl (tms) derivatives (65) and analyzed by g.l.c. to determine the correlation of the integrated area to the actual mass. The deacetylated mixture of known compounds (50-100 mg) or the reaction mixture was dissolved in dry pyridine (1 ml). Then hexamethyldisilazane (1 ml) and trimethylchlorosilane (0.5 ml) were added to the

solution. After 30 minutes the mixture was taken to dryness under reduced pressure at ∿40°C, the product triturated with methylene chloride (1 ml) and the suspension was filtered. Portions of the filtrate (20-30 μl) were injected into the gas chromatograph using a Hamilton syringe. The composition of the mixtures could be calculated on a percentage molar basis, based on the internal standard pentaerythritol. It was found that the α-D-glucopyranosides preceded the β-isomers, that in the reaction mixtures small amounts of α- and β-D-glucose were always present and that α-D-glucose had the same retention time as the ethyl, isopropyl and n-propyl α-D-glucopyranosides. However, as already mentioned by Morgan (8), the ratio of α- to β-D-glucose was constant under the standard deacetylation conditions used. Therefore the integration value for the α-isomer could be determined from that of the β-compound, which had a longer retention time than the β-D-glucopyranosides.

Retention times were found to vary slightly, depending on the concentrations of the components in the mixture, flow rate and inlet pressure of the carrier gas, and are therefore not recorded. However, the peaks in the various reaction runs were always compared with mixtures of known glucopyranosides, run under identical conditions. The results are summarized in Table III.

Table III. Yields in the formation of D-glucopyranosides from 1,2-orthoesters.

Orthoester	Conc. (mol/l)	Alcohol	Conc. (mol/l)	Catalyst	Conc. (mol/l)	Time (hrs)	Yield (%) (g.l.c.) α-OR	β-OR	glucose	Yield(%) (n.m.r.) α,β-OR
I	0.5	-	-	$SbCl_5$	0.05	0.5	8	73	11	∿quant.
"	"	-	-	"	0.1	"	28	53	10	"
"	"	Ethanol	1.0	"	"	"	44	46	8	"
"	"	"	"	"	0.5	"	82	6	4	"
XXIX	"	2-Prop.	"	"	0.1	0.5	41	52	4	"
"	"	"	"	"	0.5	"	84	5	4	"

I. Tri-0-acetyl-1,2-0-(1'-*exo*-ethoxyethylidene)-α-D-glucopyranose.

XXIX. Tri-0-acetyl-1,2-0-(1'-*exo*-n-propyloxyethylidene)-α-D-glucopyranose.

(cont'd)

Table III (cont'd)

Orthoester	Conc. (mol/l)	Alcohol	Conc. (mol/l)	Catalyst	Conc. (mol/l)	Time (hrs)	Yield (%) (g.l.c.) α-OR	β-OR	glucose	Yield(%) (n.m.r.) α,β-OR
XXIX	0.5	2-Prop.	1.0	p-TsOH	0.19	12	27	22	46	~ 50
II,IIA	0.45	"	0.9	"	0.17	"	23	24	49	"
"	0.5	"	1.0	$SbCl_5$	0.1	0.5	42	53	4	~quant.
"	"	"	0.5	"	0.5	"	85	5	9	"
"	"	"	1.0	"	"	"	86	6	4	"
"	"	Ethanol	"	"	"	"	74	17	4	"
"	"	Cyclo-hexanol	"	"	"	"	80	7	9	"
XXXVI	"	2-Prop.	"	"	"	"	81	5	6	"

II,IIA. Tri-0-acetyl-1,2-0-(2'-oxacyclopentylidene)-α-D-glucopyranose (exo, endo).

XXXVI. Tri-0-acetyl-1,2-0-cyclopentylidene-α-D-glucopyranose.

I. With Antimony Pentachloride as Catalyst.

1. From tri-O-acetyl-1,2-O-(1'-exo-ethoxyethylidene)-α-D-glucopyranose (I).

(a) This compound (0.376 g, 1.0 mmole), was dissolved in methylene chloride (2 ml). Antimony pentachloride (0.06 g, 0.2 mmole), was added and the solution was kept at room temperature for 1/2 hour. Thin layer chromatography revealed two spots with R_F values corresponding to those of ethyl tetra-O-acetyl-D-glucopyranoside and ethyl tri-O-acetyl-D-glucopyranoside. One quarter of the reaction mixture, corresponding to 0.094 g of orthoester initially, was deacetylated under standard conditions after a known amount of tetra-O-acetyl-pentaerythritol had been added, and the tms derivatives were prepared. G.l.c. analysis showed that ethyl α-D-glucopyranoside (XXIII) had been formed in 28% yield, ethyl β-D-glucopyranoside (XXIV) in 53% yield and α- and β-D-glucose in 10% yield.

Chloroform (10 ml) was added to the remaining fraction of the reaction mixture and the solution was washed with an aqueous saturated sodium bicarbonate solution (5 ml). The chloroform layer was dried by filtration through a chloroform-wetted filter paper and then evaporated to a light brown syrup. Fractionation of this syrup on a column of silicic acid (30 g) with chloroform as the eluting

solvent yielded two main fractions, which were examined by n.m.r. The syrup (90 mg) obtained from the faster moving zone contained ethyl tetra-O-acetyl-β-D-glucopyranoside (XXV) and ethyl tetra-O-acetyl-α-D-glucopyranoside (XXVI) in a ratio of about 2:1, judged by the integrations for the two sets of signals for the C-methyl protons of the ethoxy group centered at τ8.82 and τ8.78 respectively and by the intensity of the signal for the anomeric proton of XXV at τ5.55. From the slower moving band a syrup (105 mg) was isolated which comprised ethyl 3,4,6-tri-O-acetyl-β-D-glucopyranoside (XXVII) and ethyl 3,4,6-tri-O-acetyl-α-D-glucopyranoside (XXVIII) in a ratio of about 2:1, estimated from the integrations for the two sets of signals for the C-methyl protons of the ethoxy group, centered at τ8.71 and τ8.75 respectively.

(b) A further experiment with less acid catalyst was carried out. Tri-O-acetyl-1,2-O-(1'-exo-ethoxyethylidene)-α-D-glucopyranose (I) (0.376 g, 1.0 mmole), was dissolved in methylene chloride (2 ml). Antimony pentachloride (0.030 g, 0.10 mmole), was added and the solution kept for 1/2 hour at room temperature. The reaction mixture was analyzed as in the above experiment. G.l.c. indicated that ethyl β-D-glucopyranoside (XXIV) had been formed in 73% yield, ethyl α-D-glucopyranoside (XXIII) in 8% yield and α- and β-D-glucose in 11% yield.

The remaining fraction of the reaction mixture was worked up as above to yield a light yellow syrup. An ethanolic solution of this syrup was seeded with authentic ethyl tetra-O-acetyl-β-D-glucopyranoside (XXV) and crystals of the latter were obtained, 93 mg (35%), m.p. 104-107°, $[\alpha]_D^{25}$ -19° (c, 1 in chloroform).

2. From tri-O-acetyl-1,2-O-(1'-*exo*-ethoxyethylidene)-α-D-glucopyranose (I) and ethanol.

(a) Tri-O-acetyl-1,2-O-(1'-*exo*-ethoxyethylidene)-α-D-glucopyranose (I) (0.376 g, 1.0 mmole), was dissolved in methylene chloride, (1.9 ml) and dry ethanol (0.114 ml, 2 mmoles). Antimony pentachloride (0.06 g, 0.2 mmole) was added and the solution was kept at room temperature for 1/2 hour. T.l.c. revealed two spots with R_F values corresponding to those of ethyl tetra-O-acetyl-D-gluco-pyranoside and ethyl tri-O-acetyl-D-glucopyranoside. Chloroform (10 ml) was added to the reaction mixture. The solution was washed with a saturated aqueous sodium bicarbonate solution (5 ml), dried over anhydrous sodium sulfate and evaporated to a syrup *in vacuo*. Fractionation of this syrup on a column of silicic acid (30 g), employing chloroform as the eluant, yielded crystalline ethyl tetra-O-acetyl-β-D-glucopyranoside (XXV), 60 mg (16%), m.p. 105-107°, $[\alpha]_D^{25}$ - 19.5° (c, 1 in chloroform), syrupy ethyl

3,4,6-tri-O-acetyl-α-D-glucopyranoside (XXVIII), 87 mg (27%), and crystalline ethyl 3,4,6-tri-O-acetyl-β-D-glucopyranoside (XXVII), 75 mg (23%), m.p. 117-120°, $[\alpha]_D^{25}$ + 17° (c, 1 in chloroform), in that order. The n.m.r. spectra of ethyl 3,4,6-tri-O-acetyl-β-D-glucopyranoside (XXVII) and ethyl 3,4,6-tri-O-acetyl-α-D-glucopyranoside (XXVIII) are shown in Figs. 25 and 26 respectively.

The mixture of products from an identical reaction was deacetylated and the tms derivatives were prepared under standard conditions. G.l.c. showed the presence of ethyl α-D-glucopyranoside (XXIII) (44%), ethyl β-D-glucopyranoside (XXIV) (46%) and α- and β-D-glucose (8%).

(b) A further experiment with more acid catalyst was carried out. Tri-O-acetyl-1,2-O-(1'-exo-ethoxyethylidene)-α-D-glucopyranose (I) (0.376 g, 1.0 mmole) was dissolved in methylene chloride (1.85 ml) and dry ethanol (0.114 ml, 2 mmoles). Antimony pentachloride, (0.30 g, 1.0 mmole), was added and the solution was kept at room temperature for 30 minutes. After the standard work-up and fractionation on a silicic acid column, ethyl tetra-O-acetyl-α-D-glucopyranoside (XXVI), 40 mg (11%), m.p. 58-61°, $[\alpha]_D^{25}$ + 141° (c, 1 in chloroform) and ethyl 3,4,6-tri-O-acetyl-α-D-glucopyranoside (XXVIII), 160 mg (49%),

were isolated.

G.l.c. analysis of the products in an identical experiment gave the following yields: ethyl α-D-glucopyranoside (XXIII) (82%), ethyl β-D-glucopyranoside (XXIV) (6%), α- and β-D-glucose (4%).

3. Tri-O-acetyl-1,2-O-(1'-*exo*-n-propyloxyethylidene)-α-D-glucopyranose (XXIX).

This compound was prepared using the general conditions for the preparation of 1,2-orthoesters, described by Lemieux and Morgan (7). A theoretical yield of the *exo* and *endo* diastereoisomers was obtained (Table I) as judged from the n.m.r. spectrum. Crystallization from 1-propanol, with water added to turbidity, gave the *exo* isomer in 84% yield, m.p. 63-66°C. Two recrystallizations from 1-propanol-water with a trace of 2,6-lutidine yielded pure tri-O-acetyl-1,2-O-(1'-*exo*-n-propyloxyethylidene)-α-D-glucopyranose (XXIX), m.p. 68-69°C, $[\alpha]_D^{25}$ + 29° (*c*, 1 in chloroform). The n.m.r. spectrum is shown in Fig. 24 and the parameters are presented in Tables I, VII.

Anal. calcd. for $C_{17}H_{26}O_{10}$: C, 51.8; H, 6.67%; MW 390.4. Found: C, 51.7 ; H, 6.38%; MW, 392.

Lemieux and Cipera (18) reported the preparation of the title compound, m.p. 92-94.5°, $[\alpha]_D$ + 39.5° (*c*, 1 in chloroform).

4. <u>From tri-O-acetyl-1,2-O-(1'-exo-n-propyloxyethylidene)-α-D-glucopyranose (XXIX) and 2-propanol.</u>

(a) Tri-O-acetyl-1,2-O-(1'-<u>exo</u>-n-propyloxyethylidene)-α-D-glucopyranose (XXIX) (0.195 g, 0.5 mmole), was dissolved in methylene chloride (0.90 ml) and dry 2-propanol (0.075 ml, 1 mmole). Antimony pentachloride (0.03 g, 0.1 mmole), was added and the solution was kept at room temperature for 30 minutes. The reaction mixture was divided into two equal parts and one-half was deacetylated under standard conditions. After the formation of the tms derivatives the mixture was analyzed by g.l.c. The yields of the D-glucopyranosides could be calculated on a percentage molar basis. α-D-Glucopyranosides had been formed in 41% yield, β-D-glucopyranosides in 52% yield and α- and β-D-glucose in 4% yield. The ratio of the isopropyl to <u>n</u>-propyl D-glucopyranosides could not be estimated from the chromatogram, since the retention times were very similar.

The second half of the reaction mixture was subjected to n.m.r. analysis, after the standard work-up. From the integrations for the signals of the C-methyl protons in the isopropyl group centered at τ8.75 and of the C-CH_2-CH_3 protons in the <u>n</u>-propyl group centered at τ8.35 (-CH_2-) and τ8.95 (-CH_3) it was estimated that <u>n</u>-propyl D-glucopyranosides made up about 30% of the mixture.

(b) When 0.5 mmole of antimony pentachloride instead of 0.1 mmole was used in the above experiment, the g.l.c. analysis indicated the formation of α-D-glucopyranosides in 84% yield, of β-D-glucopyranosides in 5% yield and of α- and β-D-glucose in 4% yield.

5. <u>From a mixture of the epimeric tri-O-acetyl-1,2-O-(2'-oxacyclopentylidene)-α-D-glucopyranoses (II, IIA)</u>.

(a) Ethyl D-glucopyranosides.

(i) A mixture of the epimeric tri-O-acetyl-1,2-O-(2'-oxacyclopentylidene)-α-D-glucopyranoses (II, IIA), (0.187 g, 0.5 mmole), was dissolved in methylene chloride (0.90 ml) and dry ethanol (0.058 ml, 1 mmole). After the addition of antimony pentachloride (0.064 ml, 0.5 mmole), the dark solution was left at room temperature for 30 minutes. A known fraction of the mixture was deacetylated under the standard conditions, and the tms derivatives were formed. Gas chromatographic analysis indicated that the mixture contained 74% ethyl α-D-glucopyranoside (XXIII), 17% ethyl β-D-glucopyranoside (XXIV) and 4% α- and β-D-glucose.

The remainder of the reaction mixture was investigated by t.l.c. and n.m.r., after the standard work up. A thin-layer chromatogram showed the presence of only one spot with an R_F value corresponding to that of an alkyl

tri-O-acetyl-D-glucopyranoside. A comparison of the integrations for the C-methyl signals centered at $\tau 8.7$ and the pyranose ring protons indicated that ethyl D-glucopyranosides had been formed in near quantitative yield. Also apparent were the signals for 4-butyrolactone, centered at $\tau 5.6$ and $\tau 7.6$.

(b) Isopropyl D-glucopyranosides.

(i) A mixture of the epimeric tri-O-acetyl-1,2-O-(2'-oxacyclopentylidene)-α-D-glucopyranoses (II, IIA) (0.187 g, 0.5 mmole), was dissolved in methylene chloride (0.90 ml) and isopropanol (0.075 ml, 1.0 mmole). On the addition of antimony pentachloride (0.064 ml, 0.5 mmole) the solution darkened immediately. After 30 minutes the reaction mixture was worked up as indicated above and examined by t.l.c., g.l.c. and n.m.r. Thin layer chromatography showed only one compound. Gas chromatographic analysis showed that isopropyl α-D-glucopyranoside (XXX) had been formed in 86% yield, isopropyl β-D-glucopyranoside (XXXI) in 6% yield and α- and β-D-glucose in 4% yield. The n.m.r. spectrum showed that D-glucopyranosides had formed in nearly quantitative yield, judged by a comparison of the integrations for the C-methyl signals, centered at $\tau 8.75$ and the acetoxy signals. Absorption bands for 4-butyrolactone at $\tau 5.6$ and $\tau 7.6$ were also present.

In an identical experiment after the work-up, the syrup was acetylated in pyridine (2 ml) and acetic anhydride (2 ml). After 12 hours the solvents were removed in vacuo and the dark brown syrup was fractionated on a column of silicic acid (30 g), employing chloroform as the eluant. The resulting syrup was dissolved in ethanol and seeded with crystals of authentic isopropyl tetra-O-acetyl-α-D-glucopyranoside (XXXII). Recrystallization of the crystals obtained yielded pure material, m.p. 85-87°, $[\alpha]_D^{25}$ + 139° (c, 1 in chloroform), which did not show a melting point depression in admixture with authentic isopropyl tetra-O-acetyl-α-D-glucopyranoside (XXXII).

(ii) A further experiment with less acid catalyst was carried out. In this case 0.1 mmole of antimony pentachloride was used instead of 0.5 mmole. G.l.c. analysis showed that isopropyl α-D-glucopyranoside (XXX) had been formed in 42% yield, the β-isomer (XXXI) in 53% yield and α- and β-D-glucose in 4% yield.

In an identical experiment the syrupy reaction product, which had been obtained after the standard work-up, was dissolved in methylene chloride (0.90 ml). 2-Propanol (0.075 ml, 1.0 mmole), and antimony pentachloride (0.150 g, 0.5 mmole), were added and the mixture was left at room temperature for 30 minutes. After the standard

deacetylation procedure, the tms derivatives were prepared and analyzed by g.l.c. The mixture comprised isopropyl α-D-glucopyranoside (XXX) (81%), isopropyl β-D-glucopyranoside (XXXI) (9%) and α- and β-D-glucose (4%).

(iii) A reaction mixture, in which one mole of 2-propanol and one mole of antimony pentachloride per mole of orthoester were employed, was deacetylated and the tms derivatives were prepared. G.l.c. analysis showed that the mixture consisted of 85% isopropyl α-D-glucopyranoside (XXX), 5% of the β-isomer (XXXI) and 9% of α- and β-D-glucose.

(c) Cyclohexyl D-glucopyranosides.

A mixture of the epimeric tri-O-acetyl-1,2-O-(2'-oxacyclopentylidene)-α-D-glucopyranoses (II, IIA) (0.093 g, 0.25 mmole), was dissolved in methylene chloride (0.42 ml), and dry cyclohexanol (0.053 ml, 0.5 mmole). The solution turned dark brown upon addition of antimony pentachloride (0.032 ml, 0.25 mmole). After 30 minutes chloroform (10 ml) was added and the mixture was washed with a saturated aqueous sodium bicarbonate solution (5 ml). The chloroform layer was dried by filtration through a chloroform-wetted filter paper and evaporated to a syrup <u>in vacuo</u>. T.l.c. showed the presence of only one spot. The n.m.r. spectrum showed strong absorption bands

at τ8.1-9.0, indicating the incorporation of a cyclohexyl ring into the sugar molecule in high yield.

Acetylation of this material with acetic anhydride and pyridine gave a product whose n.m.r. spectrum showed the characteristic features expected for alkyl tetra-O-acetyl-α-D-glucopyranosides. Two triplets centered at τ4.50 (H-3) and τ4.65 (H-4) and a quartet centered at τ5.20 (H-2) were observed.

G.l.c. analysis of this mixture after deacetylation and preparation of the tms derivatives showed that the product consisted of cyclohexyl α-D-glucopyranoside (XXXIII) (80%), cyclohexyl β-D-glucopyranoside (XXXIV) (7%) and α- and β-D-glucose (9%). No direct comparison of the retention times of the D-glucopyranosides obtained in this reaction run to those of authentic cyclohexyl D-glucopyranosides was made, since the latter compounds were not available.

6. <u>From tri-O-acetyl-1,2-O-cyclopentylidene-α-D-glucopyranose (XXXVI) and 2-propanol</u>.

Tri-O-acetyl-1,2-O-cyclopentylidene-α-D-glucopyranose (XXXVI) (0.093 g, 0.25 mmole), was dissolved in methylene chloride (0.42 ml) and dry 2-propanol (0.037 ml, 0.5 mmole). Antimony pentachloride (0.032 ml, 0.25

mmole), was added and the solution was kept for 30 minutes at room temperature. An n.m.r. spectrum of the syrup, obtained after the normal work-up showed that isopropyl D-glucopyranosides had been formed in near quantitative yield.

The mixture was deacetylated and the tms derivatives were prepared using standard conditions. G.l.c. analysis showed that the product consisted of isopropyl α-D-glucopyranoside (XXX) (81%), isopropyl β-D-glucopyranoside (XXXI) (5%) and α- and β-D-glucose (6%).

7. Anomerizations of acetylated alkyl D-glucopyranosides.

(a) Isopropyl tetra-O-acetyl-β-D-glucopyranoside (XXXV).

This compound (0.195 g, 0.5 mmole), was dissolved in methylene chloride (0.90 ml), and 2-propanol (0.038 ml, 0.5 mmole). Antimony pentachloride (0.064 ml, 0.5 mmole), was added and the solution was kept for 30 minutes at room temperature. Chloroform (10 ml) was added, the mixture was washed with a saturated, aqueous sodium bicarbonate solution (5 ml) and dried by filtration through a chloroform-wetted filter paper. Concentration of this solution *in vacuo* yielded a syrup, the n.m.r. spectrum of which was virtually identical to that of authentic isopropyl tetra-O-acetyl-α-D-glucopyranoside (XXXII).

G.l.c. analysis of the above mixture, after deacetylation and formation of the tms derivatives, showed the presence of isopropyl α-D-glucopyranoside (XXX) (89%) and isopropyl β-D-glucopyranoside (XXXI) (5%).

(b) Ethyl 3,4,6-tri-O-acetyl-β-D-glucopyranoside (XXVII).

This compound (0.083 g, 0.25 mmole), was dissolved in methylene chloride (0.42 ml) and ethanol (0.015 ml, 0.25 mmole). Antimony pentachloride (0.032 ml, 0.25 mmole), was added and the solution kept for 30 minutes.

Acetylation of the mixture with acetic anhydride in pyridine yielded a product, the n.m.r. spectrum of which was virtually identical to that of authentic ethyl tetra-O-acetyl-α-D-glucopyranoside (XXVI).

After deacetylation of the above reaction product the tms derivatives were formed, using standard conditions. G.l.c. analysis of this mixture showed the presence of ethyl α-D-glucopyranoside (XXIII) (86%) and ethyl β-D-glucopyranoside (XXIV) (8%).

II. Formation of D-Glucopyranosides with *p*-Toluenesulfonic Acid as Catalyst.

1. From tri-O-acetyl-1,2-O-(1'-*exo*-*n*-propyloxyethylidene)-α-D-glucopyranose (XXIX) and 2-propanol.

This compound (XXIX) (0.390 g, 1.0 mmole), was dissolved in methylene chloride (2 ml), and dry 2-propanol (0.15 ml, 2 mmoles). *p*-Toluenesulfonic acid in N,N-dimethylformamide (0.15 ml, 0.38 mmole by titration), was added and the solution was kept at room temperature for 12 hours. Chloroform (10 ml) was added and one-half of the reaction mixture was washed with a saturated aqueous solution of sodium bicarbonate. Filtration through a filter paper wetted with chloroform and evaporation *in vacuo* yielded a syrup which was examined by n.m.r. From a comparison of the integrations it was estimated that *n*-propyl D-glucopyranosides had been formed in ~30% yield and isopropyl D-glucopyranosides in ~20% yield. Signals centered at τ2.2, τ2.65 and τ7.55 indicated the presence of a small amount of a *p*-tosyloxy derivative.

The remaining fraction of the reaction mixture was examined by g.l.c., using standard conditions. α-D-Glucopyranosides had been formed in 27% yield, β-D-glucopyranosides in 22% yield and α- and β-D-glucose in 46% yield.

2. <u>From the epimeric tri-O-acetyl-1,2-O-(2'-oxacyclopentylidene)-α-D-glucopyranoses (II, IIA) and 2-propanol.</u>

A mixture of II and IIA (0.125 g; 0.33 mmole), was dissolved in methylene chloride (0.65 ml), and dry 2-propanol (0.05 ml, 0.66 mmole). Dry p-toluenesulfonic acid in N,N-dimethylformamide (0.05 ml, 0.125 mmole by titration) was added and the solution was kept at room temperature for 12 hours. After the work-up, indicated in the above experiment, the mixture was examined by n.m.r. and g.l.c. The n.m.r. spectrum showed that ∿50% isopropyl D-glucopyranosides had been formed. Also apparent were signals centered at τ5.6 and τ7.6, attributed to 4-butyrolactone, and at τ2.2, τ2.65 and τ7.55, assigned to a compound bearing the p-tosyloxy function. Gas chromatographic analysis showed the presence of the following compounds: isopropyl α-D-glucopyranoside (XXX) (23%), isopropyl β-D-glucopyranoside (XXXI) (24%), α- and β-D-glucose (49%).

E. Tri-O-acetyl-1,2-O-alkylidene-α-D-glucopyranoses.

I. <u>Tri-O-acetyl-1,2-O-cyclopentylidene-α-D-glucopyranose (XXXVI).</u>

Dry p-toluenesulfonic acid in N,N-dimethyl-

formamide (0.45 ml, 1.1 mmoles by titration) was added to cyclopentanone (3 ml), containing trimethyl orthoformate (0.5 ml). The mixture was kept for 10 minutes, then subjected to a high vacuum for 10 minutes to remove the low boiling components, methanol, methyl formate, which were formed in the hydrolysis of trimethyl orthoformate. With this technique trace amounts of water could be removed from the reaction mixture.

Subsequently tri-O-acetyl-1,2-O-(1'-*exo*-ethoxyethylidene)-α-D-glucopyranose (I) (1.13 g, 3 mmoles) was added and the mixture was kept for 20 hours at room temperature. 2,6-Lutidine (1 ml) and chloroform (10 ml) were added, the solution was washed with water (2 x 10 ml) and dried by filtration through a chloroform-wetted filter paper. Evaporation of the solvents *in vacuo* gave a crystalline mass. The n.m.r. spectrum showed nearly quantitative conversion of I to the cyclopentylidene derivative (XXXVI). Two recrystallizations from ethanol yielded pure material, m.p. 113.5-115°, $[\alpha]_D^{25}$ + 34.5°, (*c*, 1 in chloroform). The n.m.r. spectrum is shown in Fig. 20 and the parameters are presented in Table IX.

Anal. Calcd. for $C_{17}H_{24}O_9$: C, 54.8; H, 6.50%. Found: C, 54.86; H, 6.42%.

II. <u>Tri-O-acetyl-1,2-O-cyclohexylidene-α-D-glucopyranose (XXXVII).</u>

Using the conditions described above, but with cyclohexanone in place of cyclopentanone, the cyclohexylidene derivative was obtained in nearly quantitative yield, judged from the n.m.r. spectrum. The syrup obtained after evaporation of the solvents was fractionated on a column of silicic acid (45 g), using 0.3% 2,6-lutidine plus 3% methanol in benzene as the eluting solvent. From the fast moving zone a syrup, 0.69 g (61%) was obtained, which could be crystallized from ethanol. One recrystallization from ethanol afforded pure material, m.p. 68-69°, $[\alpha]_D^{25}$ + 33° (c, 1 in chloroform). The n.m.r. spectrum is shown in Fig. 21 and the parameters are presented in Table IX.

Anal. Calcd. for: $C_{18}H_{26}O_9$: C, 56.0; H, 6.79%. Found: C, 56.24; H, 6.84%.

III. <u>Tri-O-acetyl-1,2-O-benzylidene-α-D-glucopyranose (XXXVIII, XXXVIIIA).</u>

Again using the above conditions, with freshly distilled benzaldehyde instead of cyclopentanone, the two diastereoisomeric benzylidene derivatives were obtained in high yield, judged from the n.m.r. spectrum. The

product was fractionated on a column of silicic acid with 0.3% 2,6-lutidine in chloroform as the eluting solvent. The resulting syrup, 0.71 g (60%) could not be induced to crystallize. The n.m.r. spectrum (Fig. 22) showed that the syrup consisted of ∿75% of one isomer and of ∿25% of the other isomer, estimated from the integrations for the signals of the protons at the benzylidene acetal carbon at τ4.13 and τ3.56 respectively. The n.m.r. parameters are presented in Table IX.

1. <u>1,2-O-Benzylidene-α-D-glucopyranose (XXXIX, XXXIXA)</u>.

Deacetylation of tri-O-acetyl-1,2-O-benzylidene-α-D-glucopyranose (XXXVIII, XXXVIIIA) with triethylamine in methanol-water yielded 1,2-O-benzylidene-α-D-glucopyranose as a crystalline mass. Two recrystallizations from methanol gave a product with melting point 157-159° C, $[\alpha]_D^{25}$ + 67.5° (*c*, 1 in methanol). The n.m.r. spectrum (in DMSO-d_6) indicated that this productwas a mixture of the two diastereoisomeric 1,2-O-benzylidene-α-D-glucopyranoses XXXIX and XXXIXA. The mixture consisted of ∿65% of one isomer and of ∿35% of the other isomer, judged from the integrations for the signals of the protons at the benzylidene acetal carbon at τ4.20 and τ3.82, respectively.

Anal. calcd. for $C_{13}H_{16}O_6$: C, 58.2; H, 6.02%. Found: C, 57.87; H, 5.85%.

IV. Tri-O-acetyl-1,2-O-isopropylidene-α-D-glucopyranose (XL).

Dry p-toluenesulfonic acid in N,N-dimethylformamide (0.3 ml, 0.73 mmole by titration) was added to freshly distilled acetone (3 ml) containing 2,2-dimethoxypropane (0.5 ml). The mixture was kept for 10 minutes, then tri-O-acetyl-1,2-O-(1'-*exo*-ethoxyethylidene)-α-D-glucopyranose (I) (0.75 g, 2 mmoles), was added. After keeping the solution 20 hours at room temperature, 2,6-lutidine (1 ml) and chloroform (10 ml) were added. The solution was washed with water (2 x 10 ml) and dried by filtration through a chloroform-wetted filter paper. Evaporation of the solvents *in vacuo* yielded a syrup, which crystallized on standing. The n.m.r. spectrum of this product showed nearly quantitative conversion of I to the isopropylidene derivative (XL). Two recrystallizations from ethanol afforded the pure title compound (XL), m.p. 86.5-88°, $[\alpha]_D^{25}$ + 26° (*c*, 1 in chloroform). The n.m.r. spectrum is shown in Fig. 23 and the parameters are presented in Table IX.

Anal. calcd. for $C_{15}H_{22}O_9$: C, 52.0; H, 6.41%. Found: C, 52.11; H, 6.43%.

Recently this compound (XL) has been reported in the literature by Rees and coworkers (42). These workers

found, m.p. 87-88°, $[\alpha]_D^{20}$ + 30.5° (c, 1 in chloroform).

V. 2-Phenyl-1,3-dioxolane (XLI).

Benzaldehyde dimethyl acetal (16.7 g, 0.11 mole), and ethylene glycol (6.2 g, 0.1 mole) were dissolved in N,N-dimethylformamide (25 ml). p-Toluenesulfonic acid (0.015 g, 0.075 mmole) was added and the flask was connected to an aspirator to remove methanol produced in the reaction. The solution was kept at 50° for one hour. Ether (100 ml) was added, the mixture was washed with a saturated aqueous solution of sodium bicarbonate and the ether layer was dried over anhydrous sodium sulfate. After evaporation of the ether, the residue was distilled through a column, b.p.$_3$ 75°, n_D^{25} 1.5255. A 20% solution of this compound XLI in deuteriochloroform provided the following n.m.r. data: a multiplet centered at τ2.45 (phenyl protons), a singlet at τ4.10 (benzylidene proton) and a multiplet centered at τ5.9 (4 methylene protons). The integration values were found to have a ratio of 5:1:4 respectively.

This compound has been prepared previously (66,67) by different methods. The observed physical constants were: bp_{760} 225° (66), bp_{11} 106-107° (67), n_D 1.5270 (67).

F. Preparation and Reactions of 1,2-Orthoesters of D-Galactopyranose and D-Mannopyranose.

I. Tri-O-acetyl-1,2-O-(1'-alkoxyethylidene)-α-D-galactopyranoses.

1. Tri-O-acetyl-1,2-O-(1'-methoxyethylidene)-α-D-galactopyranose (XLII).

Tetra-O-acetyl-α-D-galactopyranosyl bromide (56) (8.2 g, 20 mmoles), was dissolved in 2,6-lutidine (20 ml) and dry methanol (1 ml, 25 mmoles). Tetra-n-butylammonium bromide (1.5 g, 4.5 mmoles), was added and the mixture was kept at 50°C for 12 hours. Chloroform (50 ml) was added and the solution was washed with water (3 x 50 ml). The solvents were removed by azeotropic distillation with water. The syrup obtained was purified on a column of solicic acid (220 g) using 0.3% 2,6-lutidine and 3% methanol in benzene as the eluting solvent. The n.m.r. spectrum of the isolated product, 6.5 g (87%), is shown in Fig. 27 and the parameters are presented in Tables I, XI. Comparison of the integration values for the C-methyl signals at τ8.32 and τ8.41 indicated that the mixture consisted of ∿70% of the *exo* isomer and of ∿30% of the *endo* isomer.

2. Tri-O-acetyl-1,2-O-(1'-ethoxyethylidene)-α-D-galactopyranose (XLIII).

Employing the above conditions, but with ethanol instead of methanol, the diastereoisomeric ethyl orthoesters were obtained in high yield as judged from an n.m.r. spectrum. Again the product was fractionated on a column of silic acid. The n.m.r. spectrum of the syrup isolated from the fast moving zone is shown in Fig. 28 and the parameters are presented in Tables I, XI. It was estimated that the mixture comprised ∿70% of the *exo* isomer and ∿30% of the *endo* compound.

3. Tri-O-acetyl-1,2-O-(1'-benzyloxyethylidene)-α-D-galactopyranose (XLIV).

Again using the standard conditions above, but with benzyl alcohol in place of methanol, a mixture of the diastereoisomeric benzyl orthoesters was obtained in high yield. The n.m.r. spectrum, obtained after chromatographic purification, is shown in Fig. 29 and the parameters are presented in Tables I, XI. In this case the mixture consisted of ∿90-95% of the *exo* isomer and of ∿5-10% of the *endo* compound.

4. <u>1,3,4,6-Tetra-O-acetyl-α-D-galactopyranose (XLV)</u>.

(a) From tri-O-acetyl-1,2-O-(1'-ethoxyethylidene)-α-D-galactopyranose (XLIII).

This compound (XLIII) (1.5 g, 2.5 mmoles), was dissolved in 95% aqueous acetic acid (5 ml) and the reaction was followed polarimetrically. The rotation reached a constant value after 15 minutes. The mixture was freeze-dried to yield a colourless syrup, which was dissolved in ether. Addition of hexane afforded crystals of 1,3,4,6-tetra-O-acetyl-α-D-galactopyranose, 1.2 g (86%), m.p. 145-149°. One recrystallization from ether-hexane gave the pure compound, m.p. 148-150°, $[\alpha]_D^{25}$ + 142° (c, 1 in chloroform). The n.m.r. spectrum is shown in Fig. 30 and the parameters are presented in Table IV.

Anal. calcd. for $C_{14}H_{20}O_{10}$: C, 48.3; H, 5.79%. Found: C, 48.46; H, 5.61%.

1,3,4,6-Tetra-O-acetyl-α-D-galactopyranose (XLV) has been reported previously by Helferich and co-workers (68), prepared by a different method. These workers observed the following physical constants: m.p. 151°, $[\alpha]_D^{18}$ + 142.7 (c, 2.5 in chloroform).

(b) From tri-O-acetyl-1,2-O-(1'-benzyloxyethylidene)-α-D-galactopyranose (XLIV).

Palladium black (150 mg) was prehydrogenated in

dry ethyl acetate (10 ml) at room temperature and atmospheric pressure for 1 1/2 hours. Tri-O-acetyl-1,2-O-(1'-benzyloxyethylidene)-α-D-galactopyranose (XLIV) (1.1 g, 2.5 mmoles), was added and the hydrogen consumption was followed. The uptake of the theoretical amount of hydrogen (2.5 mmoles) was completed after 5 1/2 hours. Filtration and evaporation of the solvent under reduced pressure yield a syrup. Crystallization from ether-hexane gave 1,3,4,6-tetra-O-acetyl-α-D-galactopyranose (XLV), 0.75 g (86%), m.p. 143-148°. After one recrystallization from ether-hexane pure material was obtained, m.p. 148-150, $[\alpha]_D^{25}$ + 140° (c, 1 in chloroform). The melting point was undepressed in admixture with material obtained in the above experiment.

5. Tetra-O-acetyl-1-O-propionyl-β-D-galactopyranose (XLVI).

Tri-O-acetyl-1,2-O-(1'-ethoxyethylidene)-α-D-galactopyranose (XLIII) (0.55 g, 1.5 mmoles), was dissolved in dry propionic acid (3 ml) and the reaction mixture was kept at 50°C for 26 hours. After dilution with water (10 ml) the solution was extracted twice with 10 ml amounts of chloroform. The combined chloroform extracts were then washed with a saturated aqueous solution of sodium

bicarbonate (10 ml), dried over anhydrous sodium sulfate and concentrated *in vacuo* to a colourless syrup. The n.m.r. spectrum of this syrup in deuteriochloroform showed the features expected for XLVI and could readily be compared with that of penta-O-acetyl-β-D-galactopyranose. In both compounds the signal for the anomeric proton was found to be a doublet, centered at τ4.25 with a spacing of 7.5 Hz, characteristic for a diaxial relationship between H-1 and H-2 (45,46). A triplet centered at τ8.87 (C-Me) and a quartet centered at τ7.62 ($\overset{O}{\overset{\|}{C}}$-$CH_2$-C) indicated the presence of the propionyl group.

II. Reactions of Tri-O-acetyl-1,2-O-(1'-*exo*-methoxyethylidene)-β-D-mannopyranose (IV).

1. *Tri-O-acetyl-1,2-O-(1'-exo-methoxyethylidene)-β-D-mannopyranose (IV).*

This compound (IV), m.p. 111-113°, $[\alpha]_D^{25}$ -24° (*c*, 1 in chloroform), was prepared according to the directions provided by Mazurek and Perlin (25).

2. *Tetra-O-acetyl-D-mannopyranoses.*

Tri-O-acetyl-1,2-O-(1'-*exo*-methoxyethylidene)-β-D-mannopyranose (IV) (0.93 g, 2.5 mmoles), was dissolved in 95% aqueous acetic acid (3 ml) and the reaction was followed polarimetrically. When the rotation reached a

constant value after 25 minutes the reaction mixture was freeze-dried. The product was dissolved in ether and crystals of 1,3,4,6-tetra-O-acetyl-β-D-mannopyranose (XLVII), 0.29 g (32%), were obtained. Recrystallization from chloroform-ether-hexane afforded pure material, m.p. 159-160°, $[\alpha]_D^{25}$, -24° (c, 1 in chloroform). The n.m.r. spectrum is shown in Fig. 31 and the parameters are presented in Table IV.

Anal. calcd. for $C_{14}H_{20}O_{10}$: C, 48.3; H, 5.79%. Found: C, 48.63; H, 5.74%.

The mother liquors were allowed to evaporate slowly, depositing 2,3,4,6-tetra-O-acetyl-α-D-mannopyranose (XLVIII), 0.25 g (28%). After two recrystallizations the material had m.p. 92-94°, $[\alpha]_D^{25}$ + 25° (c, 1 in chloroform). The n.m.r. spectrum is shown in Fig. 32 and the parameters are presented in Table IV.

Anal. calcd. for $C_{14}H_{20}O_{10}$: C, 48.3; H, 5.79%. Found: C, 48.20; H, 5.81%.

Acetylation of compound XLVII with acetic anhydride and pyridine at 0°C yielded penta-O-acetyl-β-D-mannopyranose (XLIX). After one recrystallization from ethanol-water the melting point was found to be 116-117° and the rotation $[\alpha]_D^{25}$ -24° (c, 0.8 in chloroform). The melting point was undepressed in admixture with authentic material.

Acetylation of compound XLVIII with acetic anhydride and pyridine at 0°C yielded penta-O-acetyl-α-D-mannopyranose (L). After one recrystallization from ethanol-water this product had m.p. 72-74° and $[\alpha]_D^{25}$ + 52° (c, 1 in chloroform). The melting point was undepressed in admixture with authentic material.

1,3,4,6-tetra-O-acetyl-β-D-mannopyranose (XLVII) and 2,3,4,6-tetra-O-acetyl-α-D-mannopyranose (XLVIII) have been reported previously as products of the hydrolysis of tetra-O-acetyl-α-D-mannopyranosyl bromide (III) and chloride (69,70,71). The following physical constants were observed: Compound XLVII: m.p. 164-165°, $[\alpha]_D^{25}$ -25.2° (c, 0.52 in chloroform) (69). Compound XLVIII: m.p. 95-96°, $[\alpha]_D^{25}$ + 23.1° (c, 4.6 in chloroform)(69).

3. Tetra-O-acetyl-1-O-propionyl-α-D-mannopyranose (LI).

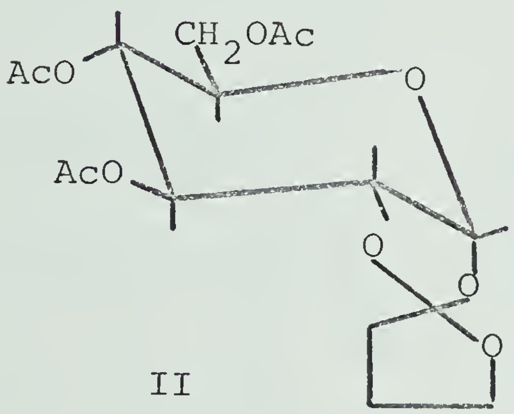
Tri-O-acetyl-1,2-O-(1'-*exo*-methoxyethylidene)-β-D-mannopyranose (IV) (0.36 g, 1 mmole), was dissolved in dry propionic acid (2 ml). After 24 hours at room temperature the mixture was diluted with water (10 ml) and extracted with chloroform (2 x 10 ml). The combined chloroform extracts were washed with a saturated aqueous solution of sodium bicarbonate, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The n.m.r. spectrum of

the product showed that only isomerization of the starting material had taken place. Evidence is based on the presence of two C-methyl signals at τ8.29 (_exo_) and τ8.51 (_endo_) and of two O-methyl signals at τ6.76 (_exo_) and τ6.55 (_endo_). Comparison of the integration values for these signals indicated that the mixture comprised the _exo_ isomer ($\sim$75%) and the _endo_ compound ($\sim$25%).

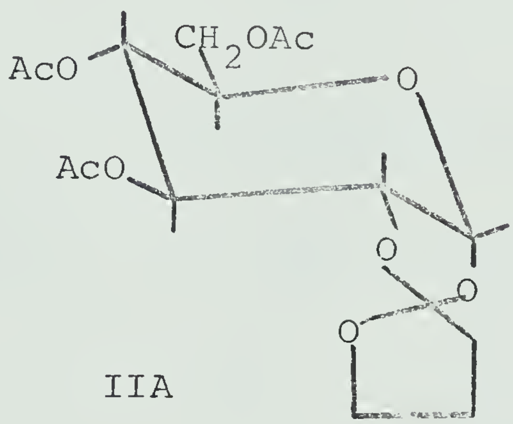
In a similar experiment the reaction mixture was kept at an elevated temperature of 50°C for 24 hours. The same workup as above yielded a colourless syrup which gave only one spot on examination by t.l.c. The n.m.r. spectrum (Fig. 33, Table IV) required the compound to be tetra-O-acetyl-1-O-propionyl-α-D-mannopyranose (LI). The optical rotation was found to be $[\alpha]_D^{25}$ + 34° (_c_, 2 in chloroform).

DISCUSSION

The main objective of this research was to prepare and examine the utility of the epimeric tri-O-acetyl-1,2-O-(2'-oxacyclopentylidene)-α-D-glucopyranoses (II, IIA) for the synthesis of D-glucopyranosides. Initially the



II



IIA

scheme outlined in Diagram 11 was envisaged for the preparation of these orthoesters.

The starting material in this reaction sequence, 1,3,4,6-tetra-O-acetyl-α-D-glucopyranose (IX) has been reported by several workers (68, 72, 73, 74). Lemieux and Huber (72) reacted 3,4,6-tri-O-acetyl-β-D-glucopyranosyl chloride with silver acetate in acetic acid to obtain IX in 81% yield. Lemieux and Morgan (74) established unequivocally that the hydrolysis of tetra-O-acetyl-β-D-glucopyranosyl chloride in acetic acid containing silver

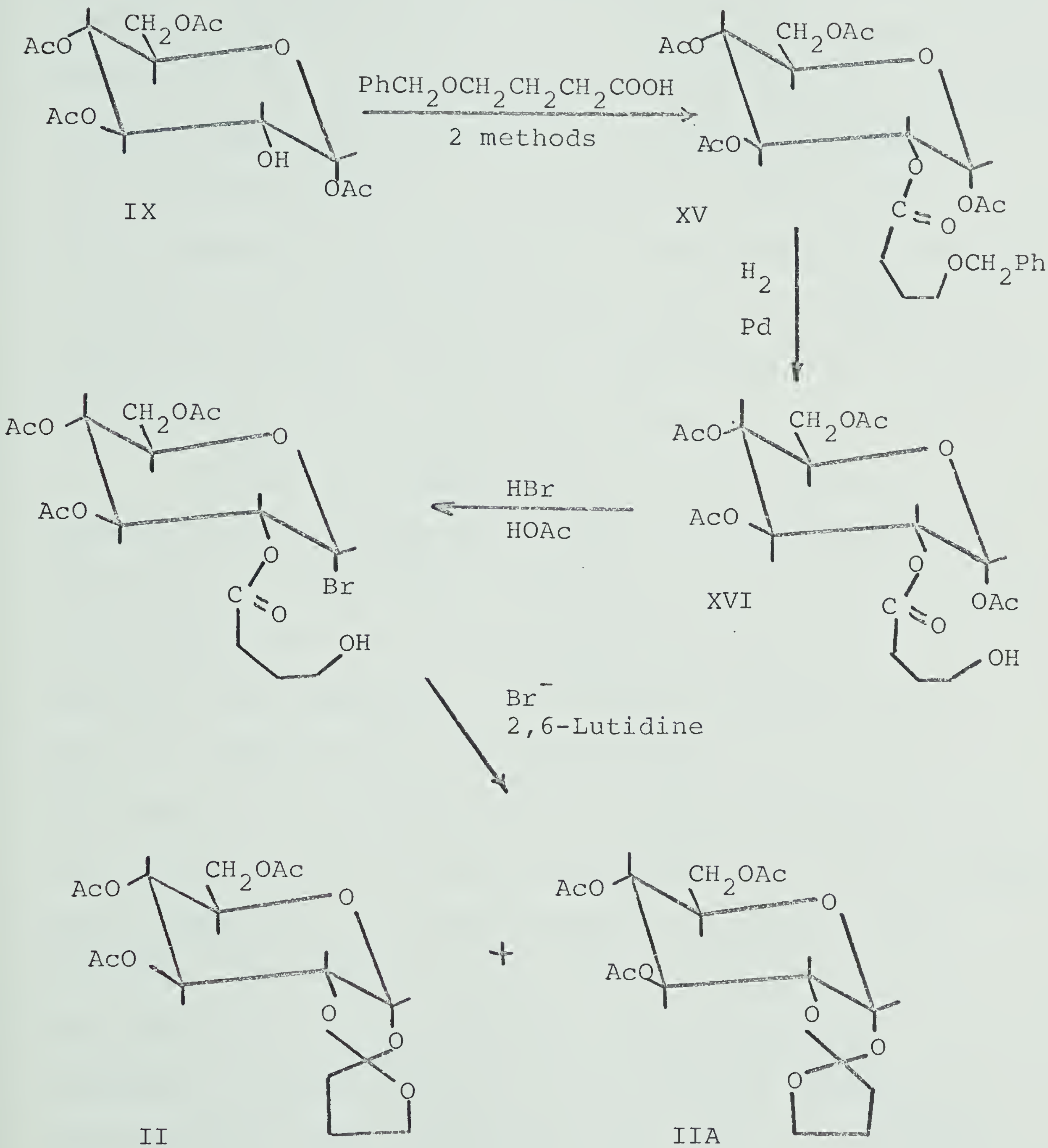
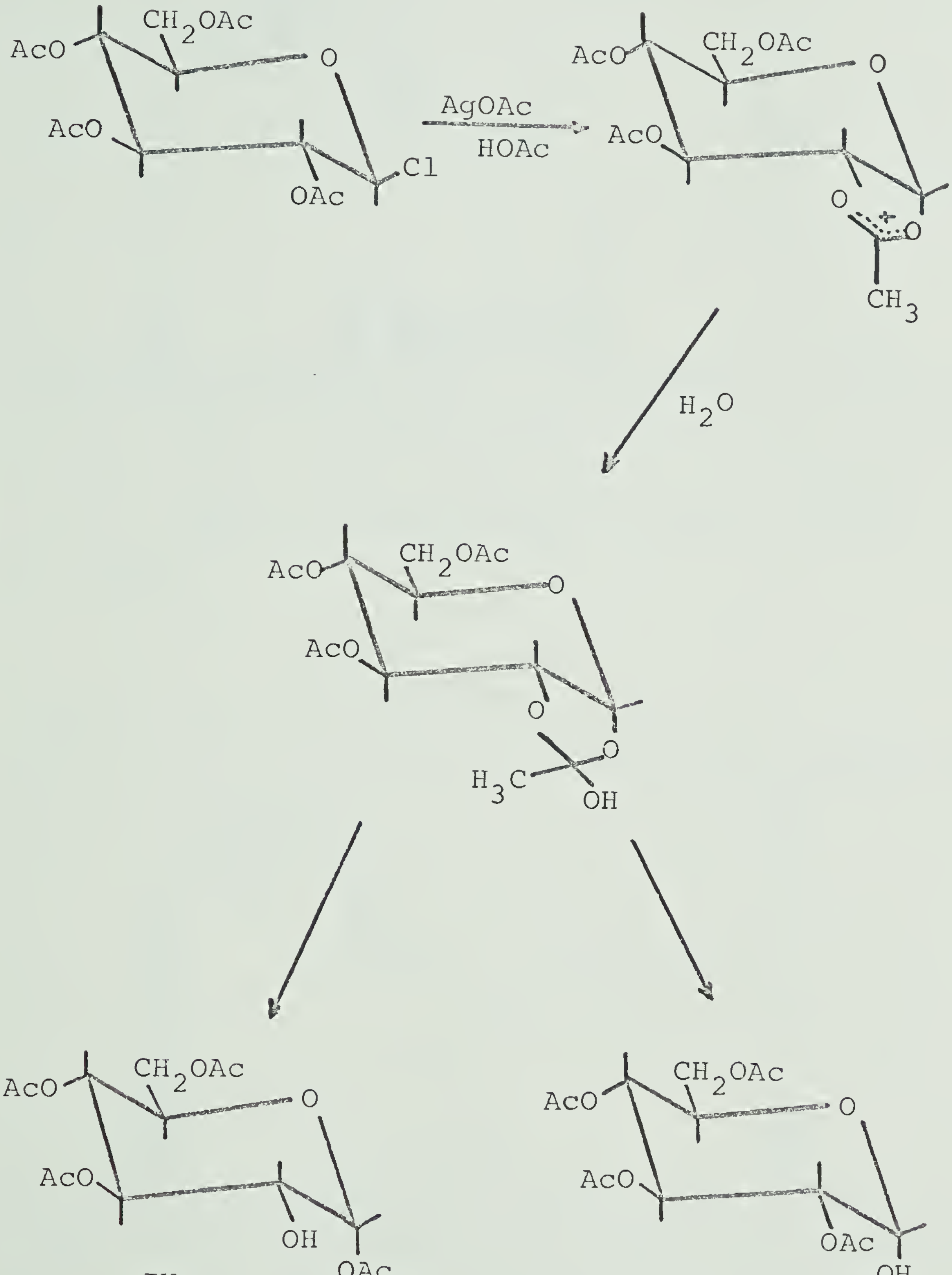


Diagram 11. Suggested route for the synthesis of the 1,2-orthoesters II, IIA.

acetate also provided 1,3,4,6-tetra-O-acetyl-α-D-glucopyranose. Earlier workers (15, 75, 76) had designated the product of this reaction, having the same physical constants as those observed by Lemieux and coworkers (72, 74), as 2,3,4,6-tetra-O-acetyl-α-D-glucopyranose (XII). Both these compounds can be expected to form from the postulated transient acid orthoester (Diagram 12). The results of Lemieux and Morgan (74) however indicated that the 1,3,4,6-tetraacetate is the major first product.

Lemieux and Cipera (18) obtained a compound designated as 2,3,4,6-tetra-O-acetyl-α-D-glucopyranose on hydrolysis of tri-O-acetyl-1,2,-O-(1'-exo-ethoxyethylidene)-α-D-glucopyranose (I) in 99% aqueous acetic acid. On repeating this experiment, but using 95% aqueous acetic acid, we obtained the same product but found it to be identical to the 1,3,4,6-tetra-O-acetyl-α-D-glucopyranose (IX) characterized by Lemieux and Morgan (74) as the product of the hydrolysis of tetra-O-acetyl-β-D-glucopyranosyl chloride. The formation of IX (79% isolated yield) by hydrolysis of the 1,2-orthoester was accompanied by the formation of about 10-15% of 2,3,4,6-tetra-O-acetyl-α-D-glucopyranose (XII) as evidenced from the n.m.r. spectrum of the crude reaction mixture. Since 1,3,4,6-tetra-O-acetyl-α-D-glucopyranose (IX) is known to isomerize to the 2,3,4,6-



IX XII

Diagram 12. Hydrolysis of tetra-O-acetyl-β-D-glucopyranosyl chloride.

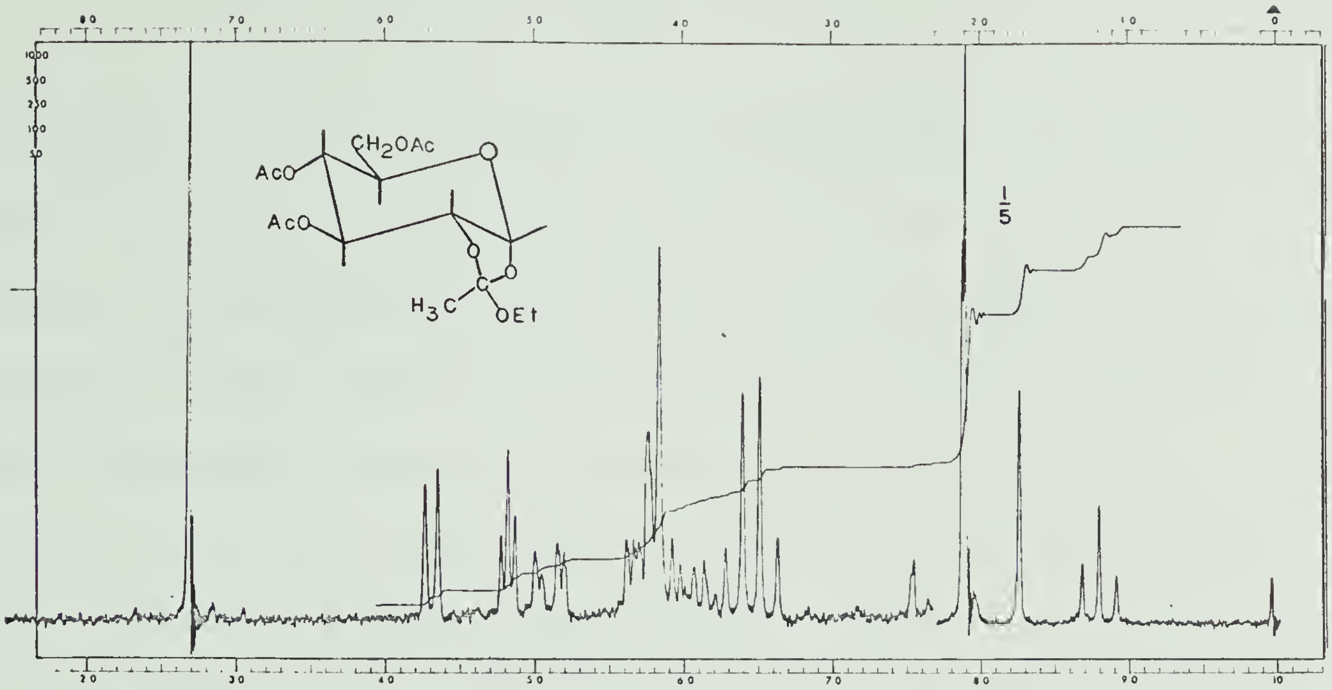


Fig. 1. N.m.r. spectrum (60 MHz) of tri-O-acetyl-1,2-O-(1'-exo-ethoxyethylidene)-α-D-glucopyranose (I) ($CDCl_3$).

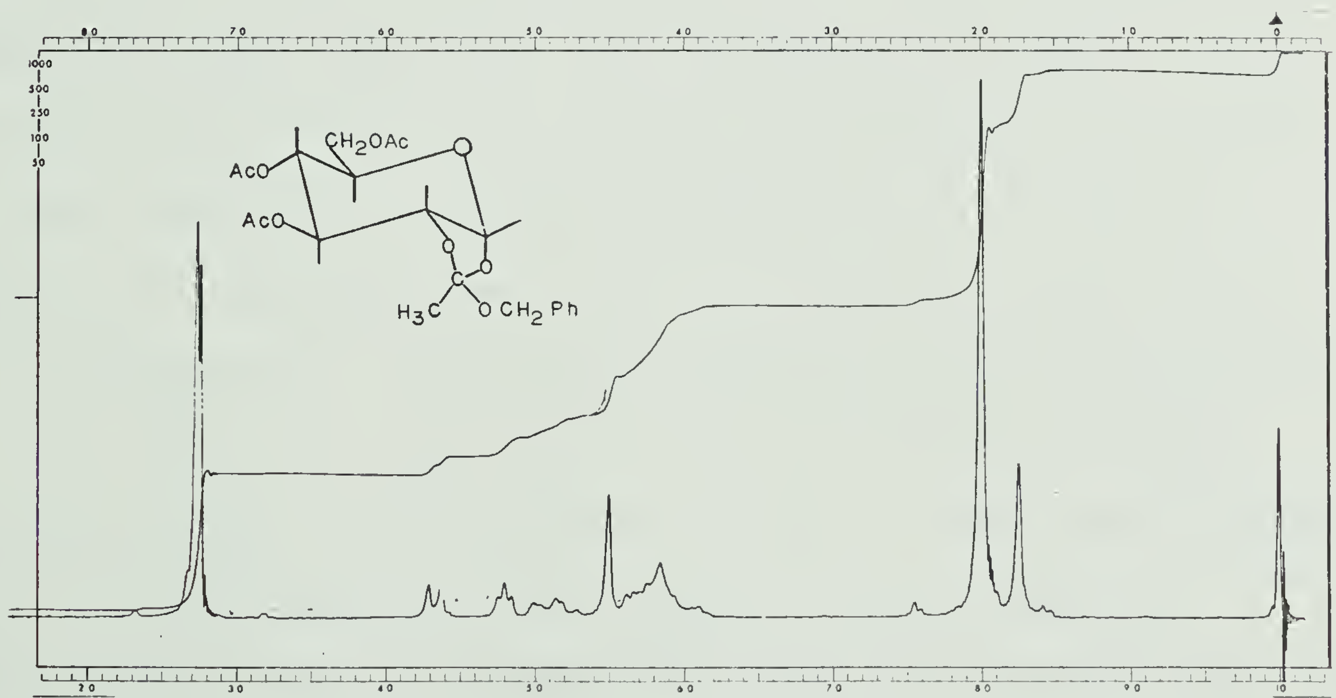


Fig. 2. N.m.r. spectrum (60 MHz) of tri-O-acetyl-1,2-O-(1'-benzyloxyethylidene)-α-D-glucopyranose (XI) ($CDCl_3$).

tetraacetate (XII) in aqueous pyridine (68, 74), the effect of 95% aqueous acetic acid was studied in this respect to determine whether the latter compound did in fact originate from the 1,3,4,6-tetraacetate (IX). We found that under the conditions employed in the reaction no isomerization had taken place after 2 hours, indicating that the 2,3,4,6-tetraacetate (XII) formed in the hydrolysis arose directly from the intermediate 1,2-orthoacid (Diagram 13). When the rotation of a solution of the 1,3,4,6-tetraacetate (IX) was followed over a longer period (10 days) an extremely slow decrease was noted. However, an n.m.r. spectrum did not show any evidence for the presence of a compound other than the 1,3,4,6-tetraacetate (IX). It is of interest to note that Paulsen and coworkers (77) claim to have observed the isomerization of 2,3,4,6-tetra-O-acetyl-α-D-glucopyranose (XII) to 1,3,4,6-tetra-O-acetyl-α-D-glucopyranose (IX) during recrystallization procedures.

The n.m.r. spectrum of 1,3,4,6-tetra-O-acetyl-α-D-glucopyranose (IX) is shown in Fig. 3. The broad signal at τ7.0 was assigned to the hydroxyl proton since it disappeared when the chloroform solution was shaken with D_2O. The coupling of the hydroxyl proton with H-2 could be observed well when DMSO-d_6 was used as solvent. The 100 MHz spectrum of this solution is shown in the inset of Fig. 3.

The signal for the hydroxyl proton appears as a doublet with splitting of 6.4 Hz at τ4.05. Irradiation at the resonance frequency of H-2 (τ5.85) collapses this doublet as well as the doublet for H-1 (τ3.65) and the triplet for H-3 (τ4.50).

In order to more firmly establish the intermediacy of the 1,2-orthoacid, tri-O-acetyl-1,2-O-(1'-benzyloxy-ethylidene)-α-D-glucopyranose (XI) was prepared. This compound was obtained as a syrup; the structure was verified by the n.m.r. spectrum (Fig. 2). On hydrogenolysis in neutral solution (conditions wherein hydrolysis was shown not to take place), the 1,3,4,6-tetraacetate (IX) was formed in 62% yield. The n.m.r. spectrum of the crude reaction product was virtually identical to the one obtained from the hydrolysis product of tri-O-acetyl-1,2-O-(1'-exo-ethoxyethylidene)-α-D-glucopyranose (I) (Exp. C.I.3.(a)(i)), indicating the presence of about 85% 1,3,4,6-tetraacetate (IX) and of about 15% 2,3,4,6-tetraacetate (XII). Again, it was shown that the two latter compounds did not isomerize under the reaction conditions. However, when a few drops of 2,6-lutidine were added in the above hydrogenation experiment, the main products were found to be the 2,3,4,6-tetra-O-acetyl-D-glucopyranoses (XII, XIIA), as indicated by the n.m.r. spectrum (Fig. 4). This is in

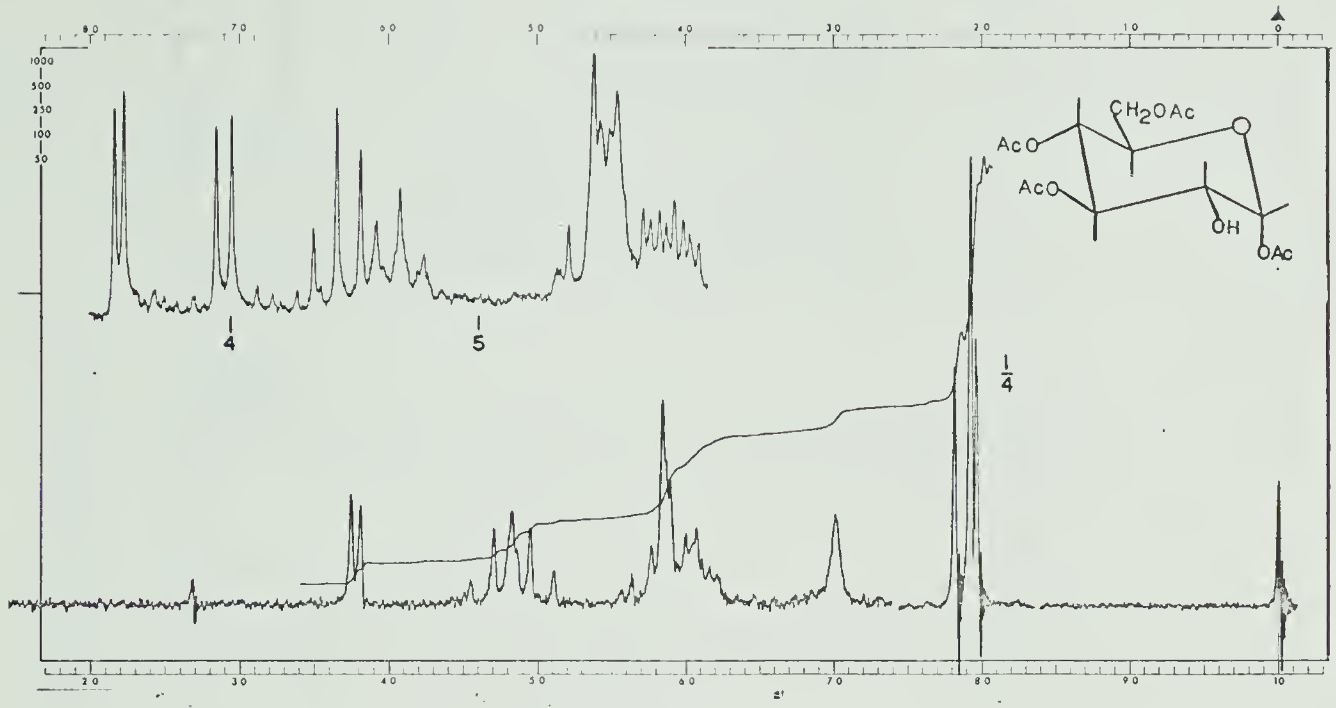


Fig. 3. N.m.r. spectrum (60 MHz) of 1,3,4,6-tetra-O-acetyl-α-D-glucopyranose (IX) ($CDCl_3$). Inset (100 MHz) (DMSO-d_6).

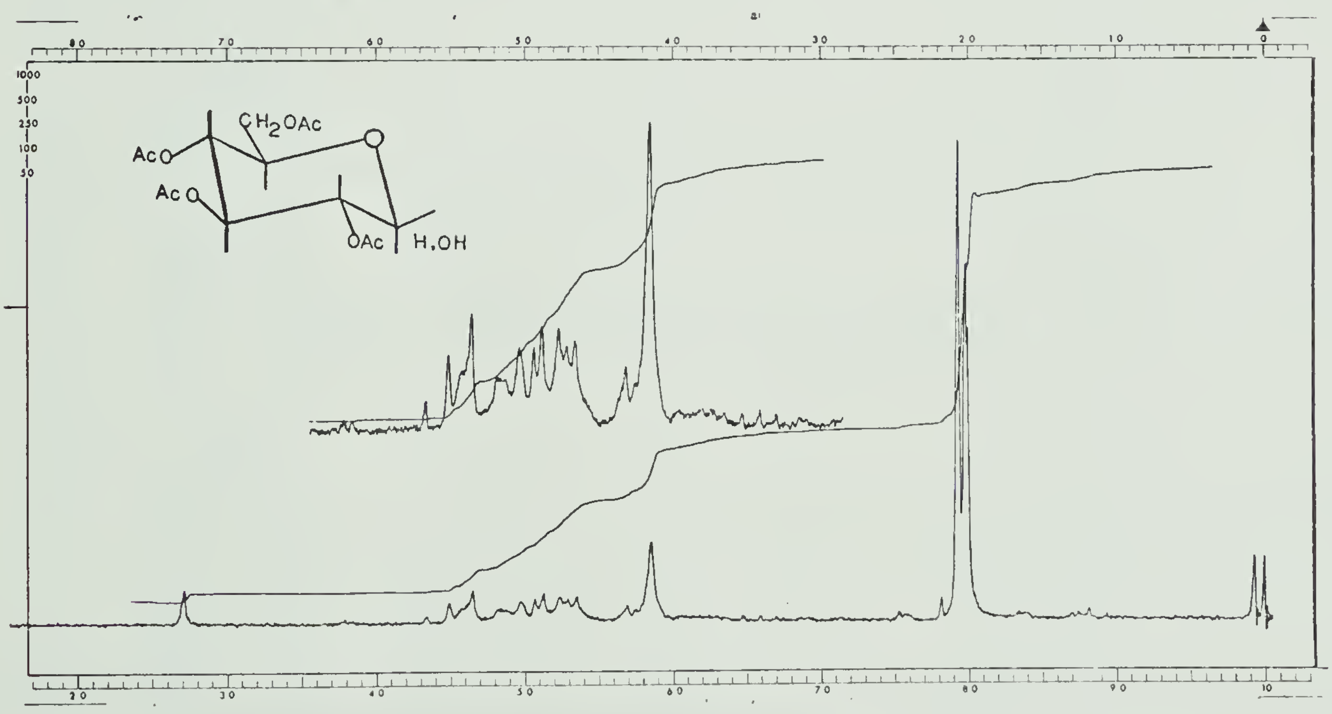


Fig. 4. N.m.r. spectrum (60 MHz) of 2,3,4,6-tetra-O-acetyl-D-glucopyranose (XII, XIIA) ($CDCl_3$).

Table IV. N.m.r. parameters (60 MHz, $CDCl_3$) of acylated D-hexopyranoses.

	H-1 (τ)	$J_{1,2}$ (Hz)	H-2 (τ)	$J_{2,3}$ (Hz)	H-3 (τ)	$J_{3,4}$ (Hz)	H-4 (τ)	$J_{4,5}$ (Hz)	OAc (τ)
IX	3.76	4.0	6.12	9.5	4.7	9.5	4.95	9.5	7.82, 7.93(2) 7.98
XIII	4.30	7.0	4.8-5.0	-	4.8-5.0	-	4.8-5.0	-	7.93(s), 8.0(m)
XLV	3.67	4.0	~5.95	10.5	4.80	3.5	4.50	1.5	7.82, 7.85 7.94, 7.96
XLVII	4.19	1.0	5.7-5.9	3.0	4.98	9.5	4.60	9.5	7.82, 7.89 7.91, 7.96
XLVIII	-	-	-	-	-	-	-	-	7.80, 7.86 7.92, 7.97
LI	3.95	1.5	-	-	-	-	-	-	7.84, 7.94 7.96, 8.02

IX. 1,3,4,6-Tetra-O-acetyl-α-D-glucopyranose.
XIII. Tetra-O-acetyl-1-O-propionyl-β-D-glucopyranose.
XLV. 1,3,4,6-Tetra-O-acetyl-α-D-galactopyranose.
XLVII. 1,3,4,6-Tetra-O-acetyl-β-D-mannopyranose.
XLVIII. 2,3,4,6-Tetra-O-acetyl-α-D-mannopyranose.
LI. Tetra-O-acetyl-1-O-propionyl-α-D-mannopyranose.

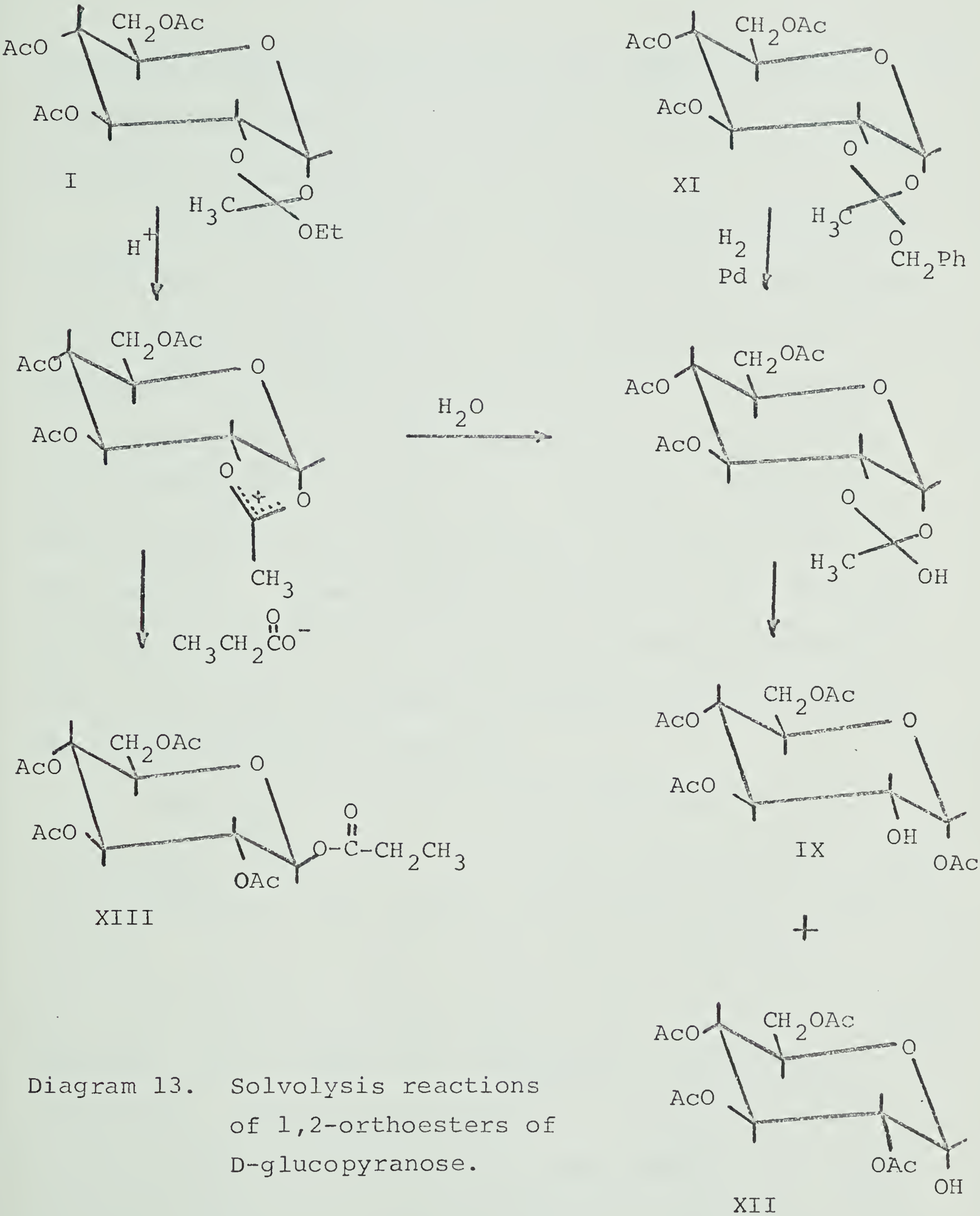


Diagram 13. Solvolysis reactions of 1,2-orthoesters of D-glucopyranose.

accord with the observation (68, 74) that the 1,3,4,6-tetraacetate isomerizes very fast to the 2,3,4,6-tetra-acetate in basic solution (XII, XIIA).

The above results seem to support the conclusion of Lemieux and coworkers (18, 74) that the 1,2-orthoacid is in fact an intermediate in the hydrolysis of 1,2-orthoesters and compounds which produce an intermediate 1,2-acetoxonium ion. Thus the solvent is not involved as a nucleophilic reagent (78). Although a compound of the 1,2-orthoacid type has not been isolated as yet (79, 80) recently spectroscopic evidence has been obtained for the existence of an acid trifluoroacetic orthoester (81), when cis-3,4-dihydroxy-tetrahydrofuran was treated with trifluoroacetic anhydride.

The results obtained in the hydrolysis of 1,2-orthoesters require that the 1,2-orthoacid prefers to open in the direction which places the acetoxy group at the 1-position. King and Albutt (82) made the observation that the hydrolysis of acyloxonium salts in which the five-membered ring is fused to a trans-decalin system gave exclusively (>99.5%) the compound in which the acyloxy group is axial and the hydroxyl group equatorial. This was also observed in the hydrolysis of orthoesters of the same type. These workers feel that a significant factor

in the opening of the intermediate orthoacid is the energy of the repulsive non-bonding interactions that arise if the equatorial ester is formed. Although these suggestions would explain our results obtained in the D-glucose and D-galactose series they do not hold true for D-mannose, in which case the two isomers were obtained in a ratio of about 1:1 (discussed later).

It seemed interesting to react tri-O-acetyl-1,2-O-(1'-exo-ethoxyethylidene)-α-D-glucopyranose (I) with dry propionic acid or acetic acid (18). The products were found to be tetra-O-acetyl-1-O-propionyl-β-D-glucopyranose (XIII) and penta-O-acetyl-β-D-glucopyranose respectively. When the change of the optical rotation was followed, it was noted that the reactions proceeded very slowly, compared

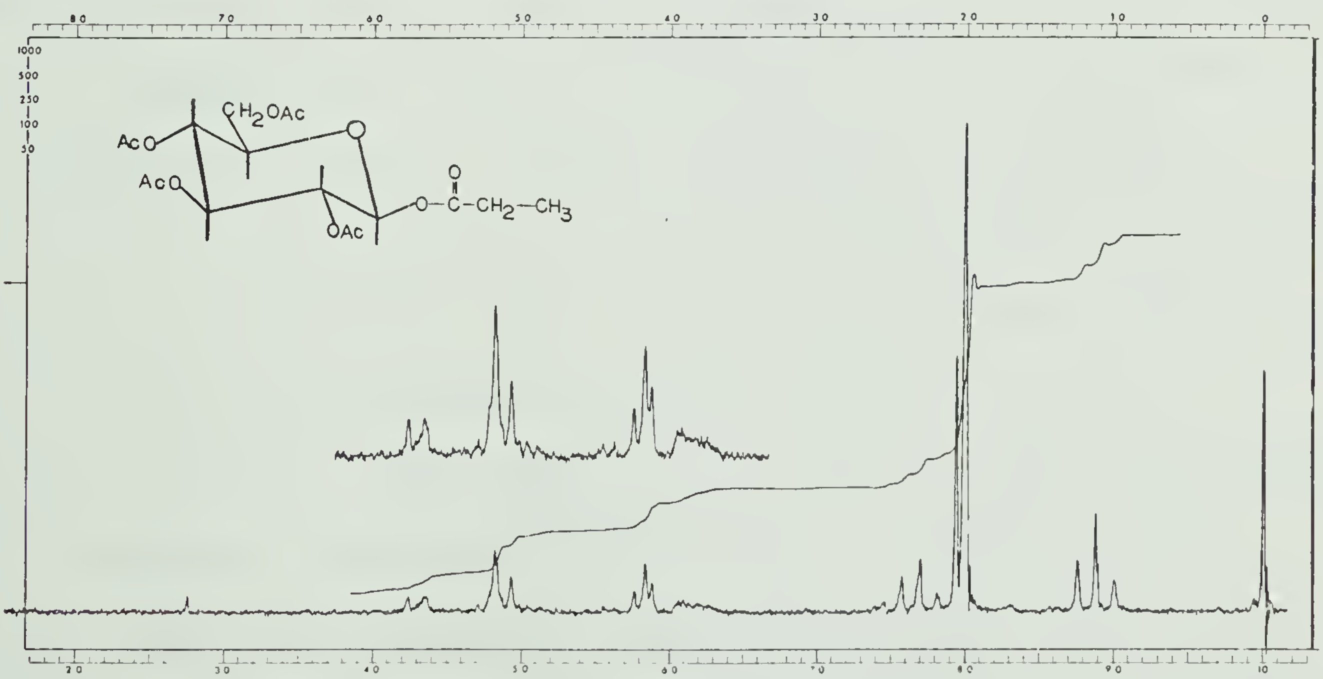
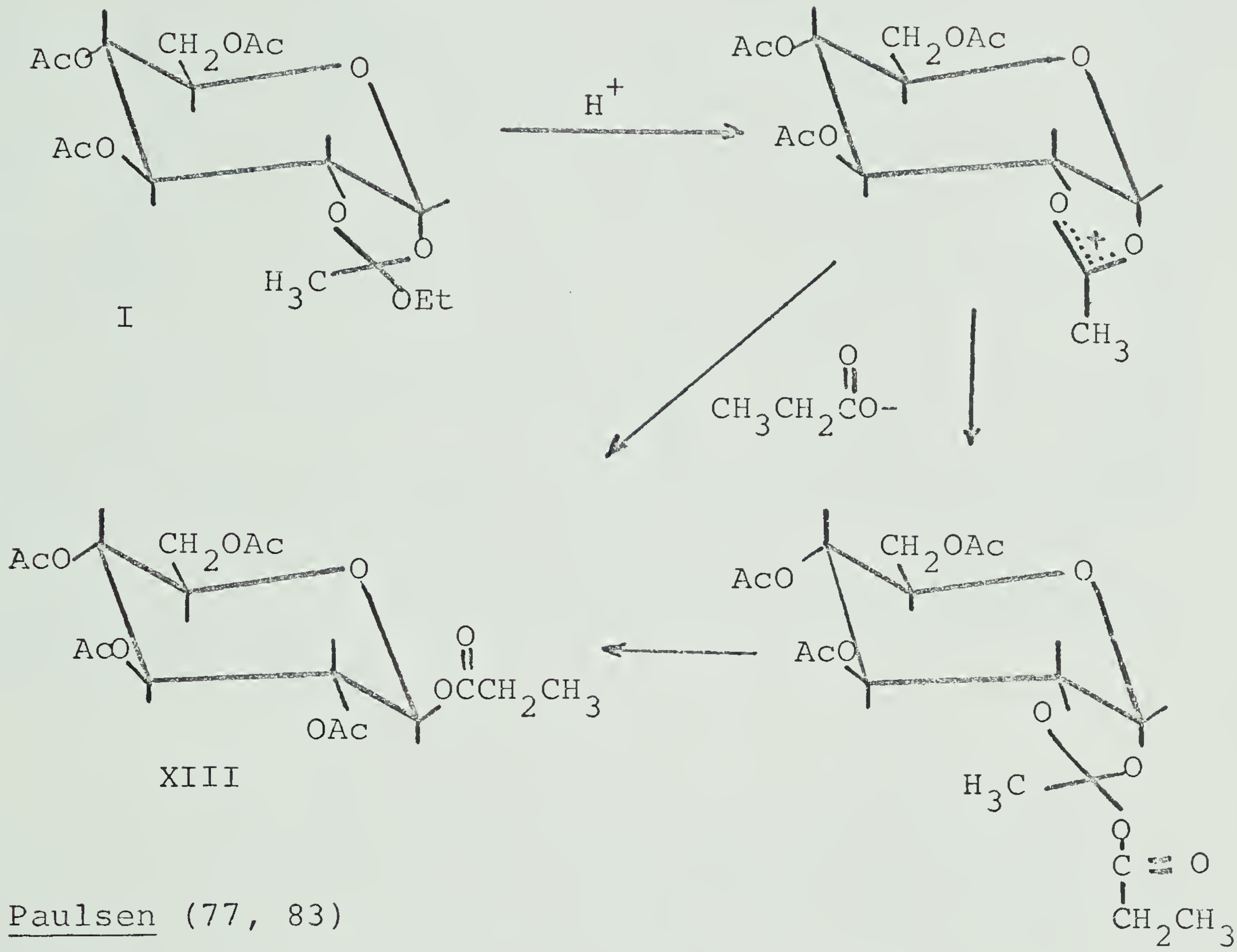


Fig. 5. N.m.r. spectrum (60 MHz) of tetra-O-acetyl-1-propionyl-β-D-glucopyranose (XIII) ($CDCl_3$).

to the hydrolysis of I in 95% aqueous acetic acid. The suggested mechanism for the formation of XIII is outlined in Diagram 14. In this respect it is of interest to note the formation of penta-O-acetyl-α-D-glucopyranose (XVII) in the reaction of tri-O-acetyl-α-D-glucopyranose 1,2-acetoxonium hexachloroantimonate with dry acetic acid, performed by Paulsen and coworkers (77, 83). It can be visualized, however, that the β-anomer is formed first and then anomerizes under the strongly acidic reaction conditions.

The reason for developing a convenient synthesis of 1,3,4,6-tetra-O-acetyl-α-D-glucopyranose (IX) was to have available starting material for the preparation of tetra-O-acetyl-2-O-(4'-benzyloxybutyryl)-α-D-glucopyranose (XV) (Diagram 11). For the synthesis of 4-benzyloxybutyric acid (XIV) we devised a method analogous to procedures described in the literature for the preparation of phenyloxybutyric acids (84, 85). 4-Butyrolactone was heated with sodium benzyloxide in benzyl alcohol to give 4-benzyloxybutyric acid (XIV) in 41% yield. This modification was necessary since we obtained only a very low yield (<5%) when we followed the instructions published by Haga (58), who heated 4-butyrolactone with potassium hydroxide and benzyl alcohol.



I

XIII

Paulsen (77, 83)

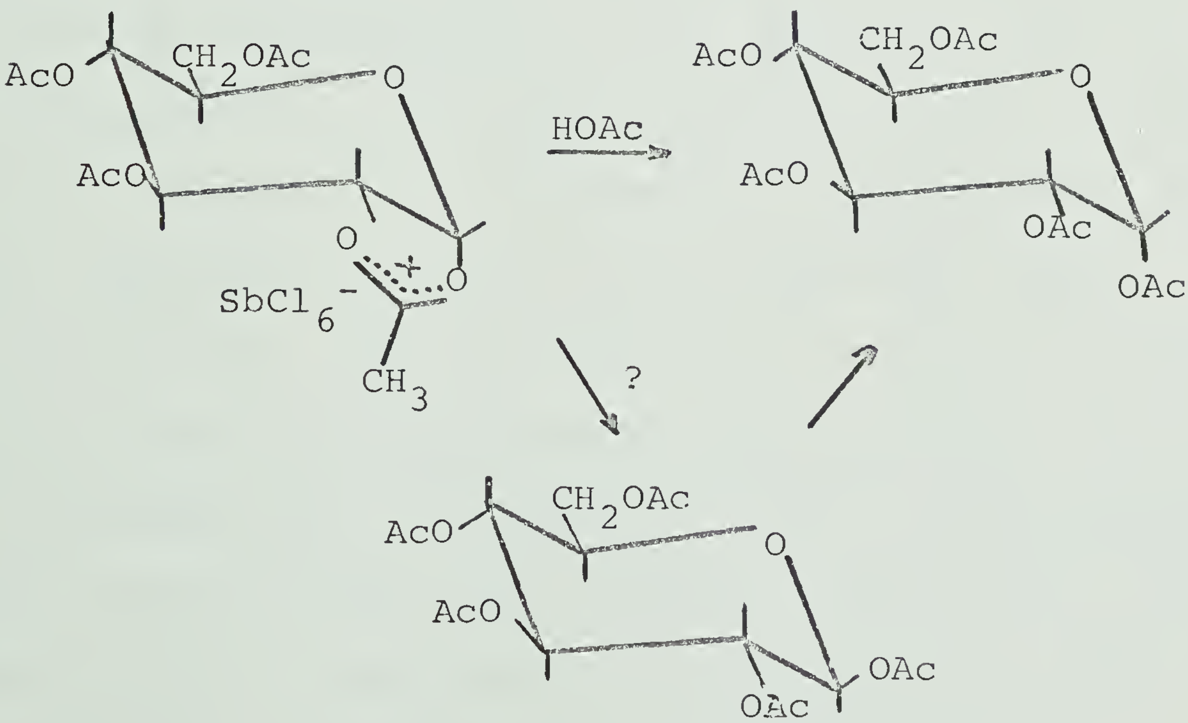


Diagram 14.

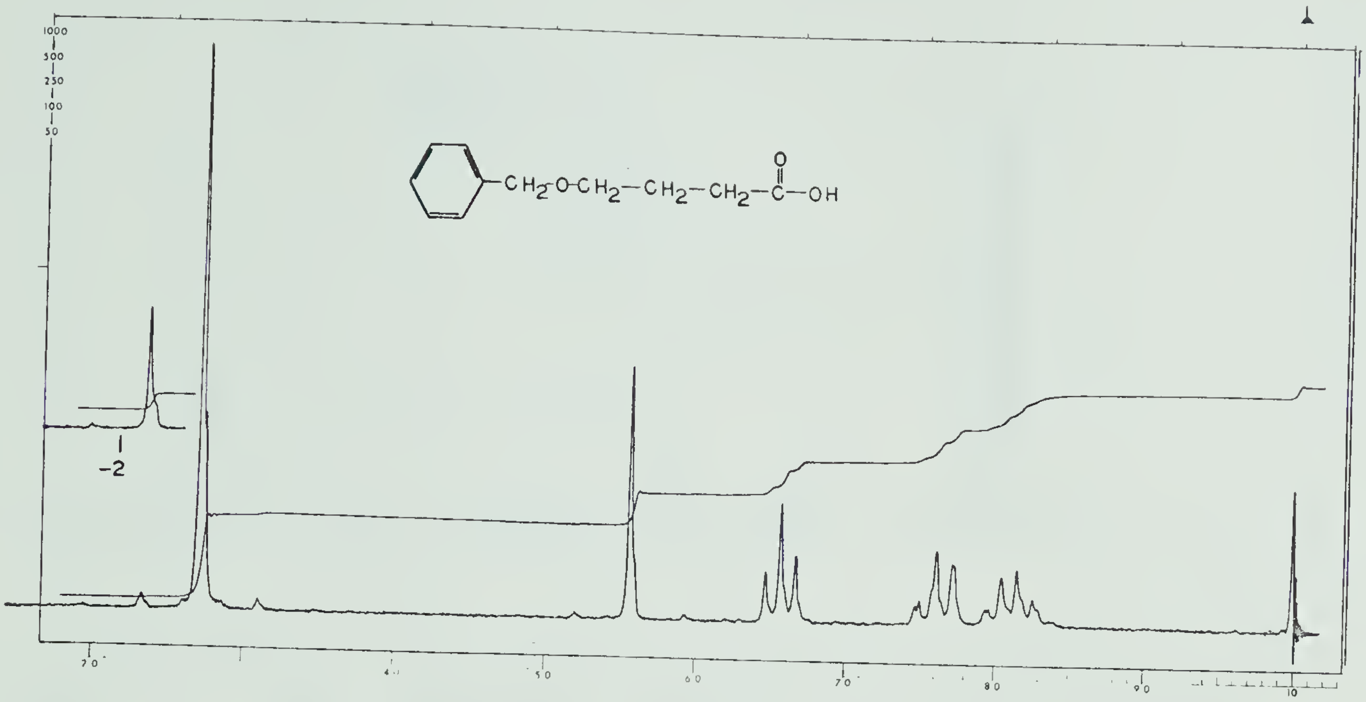


Fig. 6. N.m.r. spectrum (60 MHz) of 4-benzyloxybutyric acid (XIV) ($CDCl_3$).

1,3,4,6-Tetra-O-acetyl-α-D-glucopyranose (IX) was esterified with 4-benzyloxybutyric acid (XIV) either with dicyclohexylcarbodiimide as the condensing agent or analogously to a procedure described by Human and Mills (86). Using the latter method the acid chloride (XIVA) was prepared in solution and the sugar was added subsequently. This precaution had to be taken since we found that 4-benzyloxybutyryl chloride (XIVA) could not be isolated pure; it cyclized to give 4-butyrolactone and benzyl chloride upon attempted distillation. The distillate was examined by n.m.r. and g. l.c. and its composition was unequivocally established.

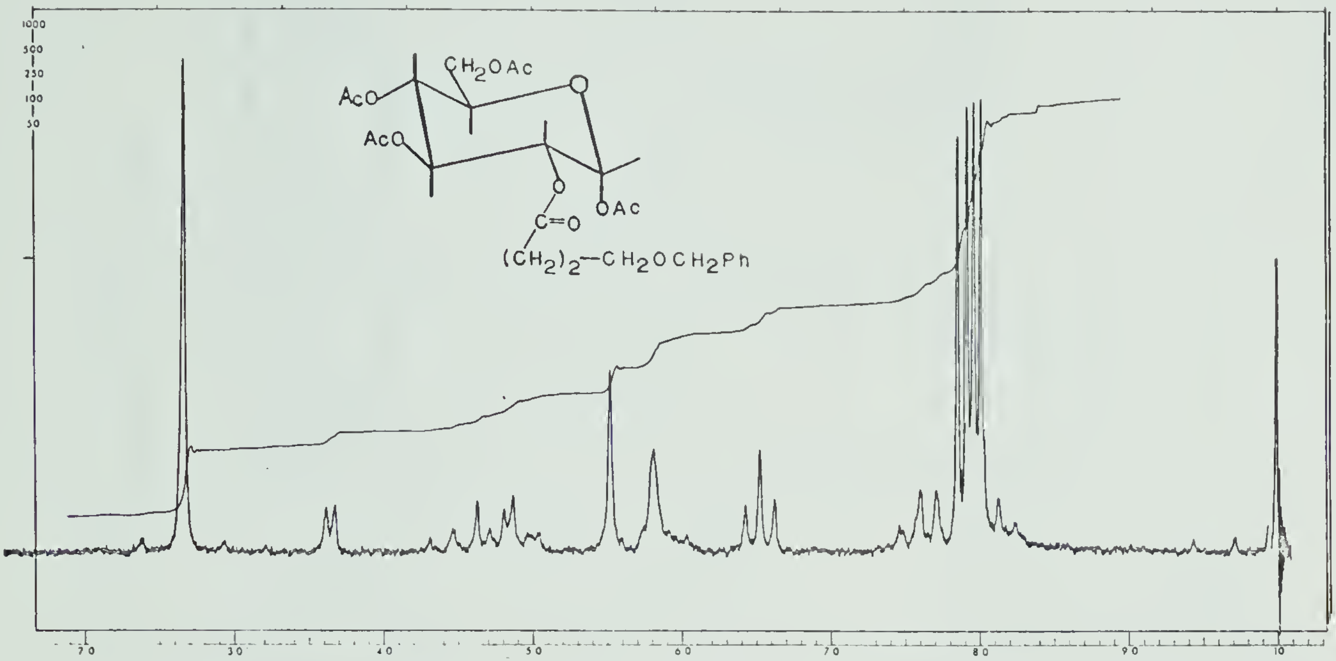


Fig. 7. N.m.r. spectrum (60 MHz) of tetra-O-acetyl-2-O-(4'-benzyloxybutyryl)-α-D-glucopyranose (XV) ($CDCl_3$).

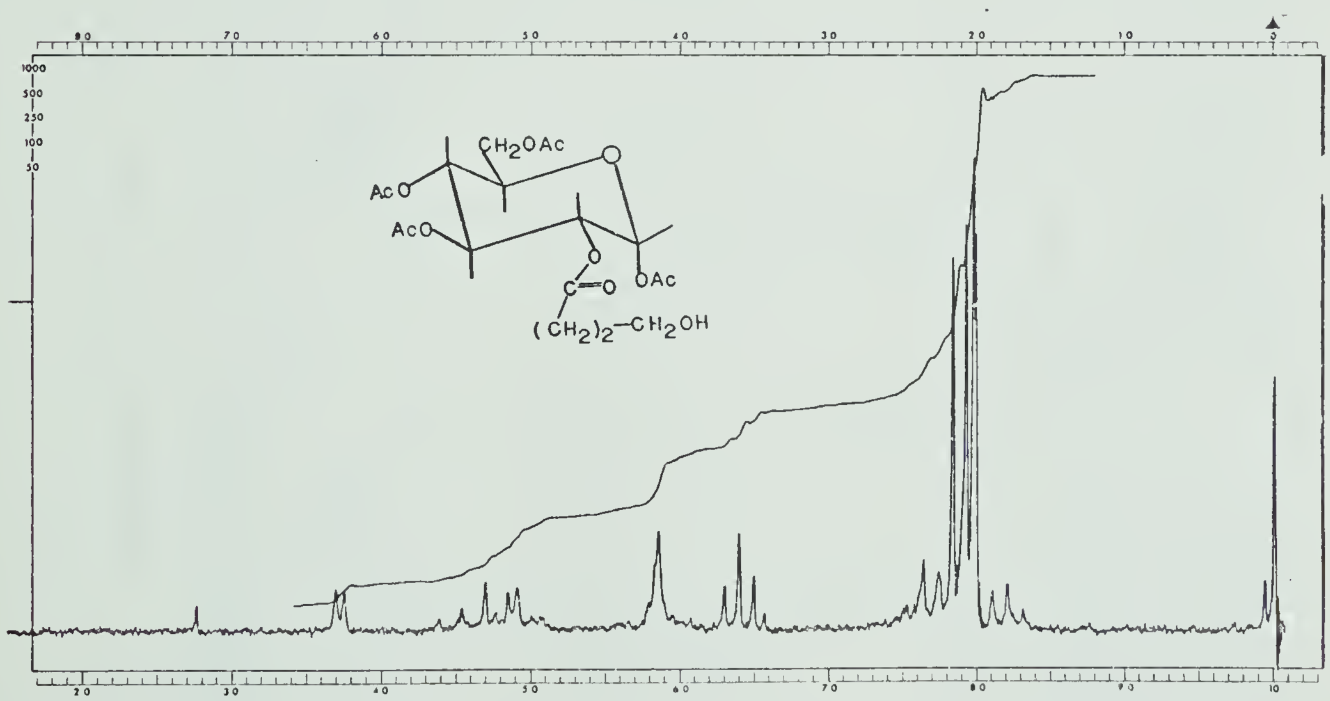


Fig. 8. N.m.r. spectrum (60 MHz) of tetra-O-acetyl-2-O-(4'-hydroxybutyryl)-α-D-glucopyranose (XVI) ($CDCl_3$).

Table V. N.m.r. parameters (60 MHz, $CDCl_3$) of acylated α-D-glucopyranoses and α-D-glucopyranosyl halides.

	H-1 (τ)	$J_{1,2}$ (Hz)	H-2 (τ)	$J_{2,3}$ (Hz)	H-3 (τ)	$J_{3,4}$ (Hz)	H-4 (τ)	CH_2(a) (τ)	CH_2(b) (τ)	CH_2(c) (τ)
XIV	-	-	-	-	-	-	-	6.62	8.15	7.63
XV	3.62	3.5	∿4.9	9.5	4.45	9.5	∿4.85	6.52	∿8.1	7.60
XVI	3.71	3.5	∿4.95	9.5	4.53	9.5	∿4.9	6.40	8.15	7.65
XIX	3.40	4.0	5.19	9.5	4.46	9.5	∿4.85	-	-	-

Numbering system for 4'-benzyloxybutyryl group: $PhCH_2\text{-}O\text{-}\overset{a}{CH_2}\text{-}\overset{b}{CH_2}\text{-}\overset{c}{CH_2}\text{-}COOH$.

XIV. 4-Benzyloxybutyric acid.

XV. Tetra-O-acetyl-2-O-(4'-benzyloxybutyryl)-α-D-glucopyranose.

XVI. Tetra-O-acetyl-2-O-(4'-hydroxybutyryl)-α-D-glucopyranose.

XIX. Tri-O-acetyl-2-O-propionyl-α-D-glucopyranoxyl bromide.

(cont'd)

Table V (cont'd)

	H-1 (τ)	$J_{1,2}$ (Hz)	H-2 (τ)	$J_{2,3}$ (Hz)	H-3 (τ)	$J_{3,4}$ (Hz)	H-4 (τ)	CH_2(a) (τ)	CH_2(b) (τ)	CH_2(c) (τ)
XX	3.85	4.0	6.1	9.5	4.68	9.5	4.95	-	-	-
XXI	3.75	4.0	5.02	9.5	4.41	9.5	4.87	6.54	∿8.1	7.56
X	3.71	4.0	4.95	9.5	4.42	9.5	4.9	6.33	8.15	7.55
XXII	4.27	5.5	-	3.0	4.81	3.0	5.1	∿6.5	∿8.1	∿7.6

XX. 3,4,6-Tri-0-acetyl-α-D-glucopyranosyl chloride.

XXI. Tri-0-acetyl-2-0-(4'-benzyloxybutyryl)-α-D-glucopyranosyl chloride.

X. Tri-0-acetyl-2-0-(4'-hydroxybutyryl)-α-D-glucopyranosyl chloride.

XXII. Tri-0-acetyl-1,2-0-(1'-methoxy-4'-benzyloxybutyryl)-α-D-glucopyranose.

Tetra-O-acetyl-2-O-(4'-benzyloxybutyryl)-α-D-glucopyranose (XV) was obtained as a crystalline compound with the n.m.r. spectrum shown in Fig. 7. The parameters (Tables V, VI) of the ring protons can be compared readily with those of analogous protons in penta-O-acetyl-α-D-glucopyranose (XVII) (Table VI).

Table VI. N.m.r. parameters of penta-O-acyl-α-D-glucopyranoses (XV, XVII).

	H-1 (τ)	$J_{1,2}$ (Hz)	H-2 (τ)	$J_{2,3}$ (Hz)	H-3 (τ)	$J_{3,4}$ (Hz)	H-4 (τ)
XV	3.62	3.5	4.9	9.5	4.45	9.5	∿4.85
XVII	3.62	3.5	∿4.9	9.5	4.45	9.5	∿4.85

Spectra taken at 60 MHz in $CDCl_3$ solution.

The protective benzyloxy group in compound XV was removed by catalytic hydrogenation in methanol, yielding tetra-O-acetyl-2-O-(4'-hydroxybutyryl)-α-D-glucopyranose (XVI). The n.m.r. spectrum of XVI (Fig. 8, Table V) closely resembles that of XV and was taken as proof of the structure.

In attempting to synthesize the diastereoisomeric tri-O-acetyl-1,2-O-(2'-oxacyclopentylidene)-α-D-glucopyranoses (II, IIA) it was first necessary to prepare tri-O-acetyl-2-O-(4'-hydroxybutyryl)-α-D-glucopyranosyl bromide and then to react this compound with tetra-n-butylammonium bromide and 2,6-lutidine according to Lemieux and Morgan (7). The addition of bromide ions is required since these are believed to catalyze the anomerization of the α-bromide to the β-isomer (22) (Diagram 15).

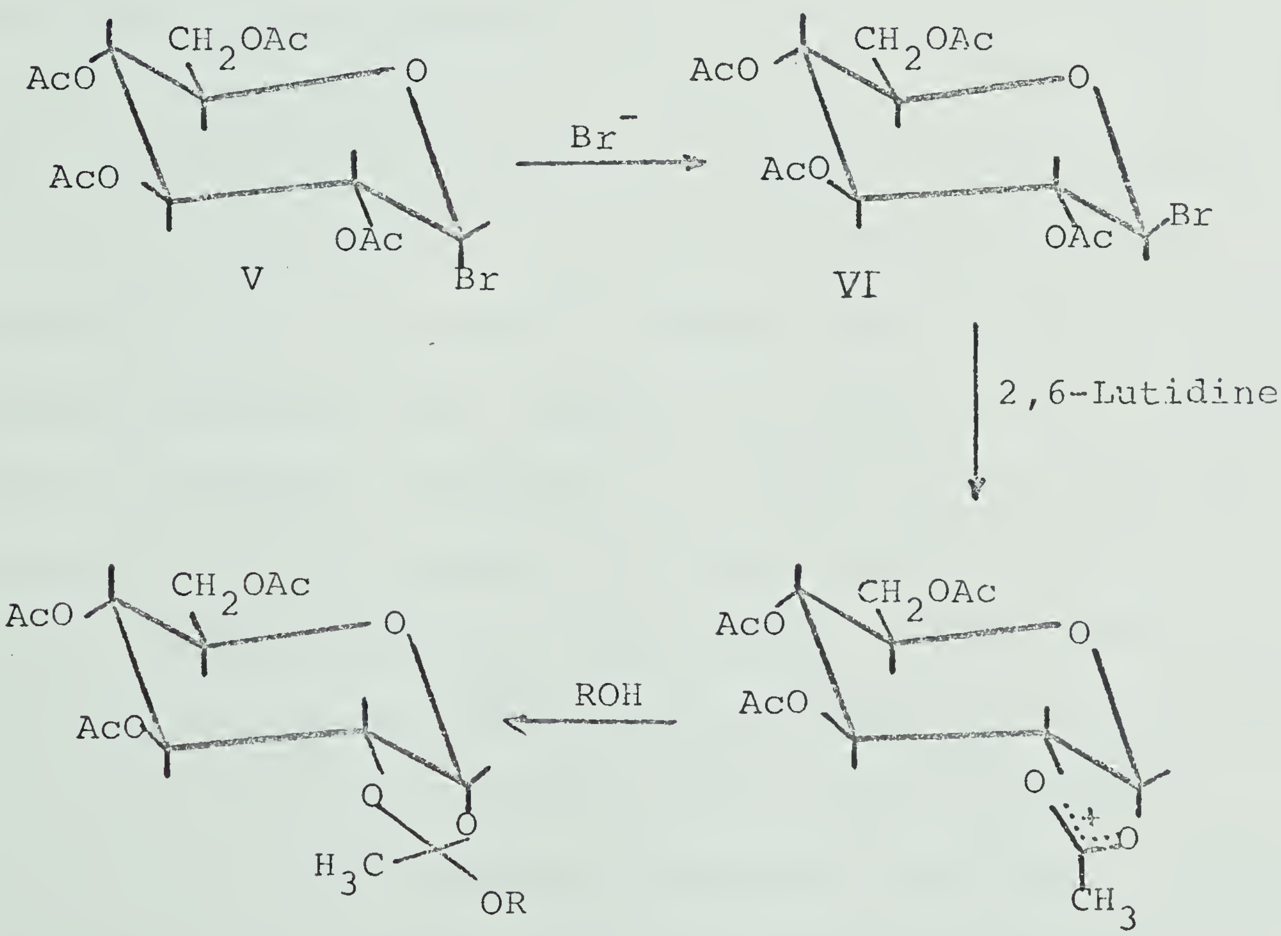
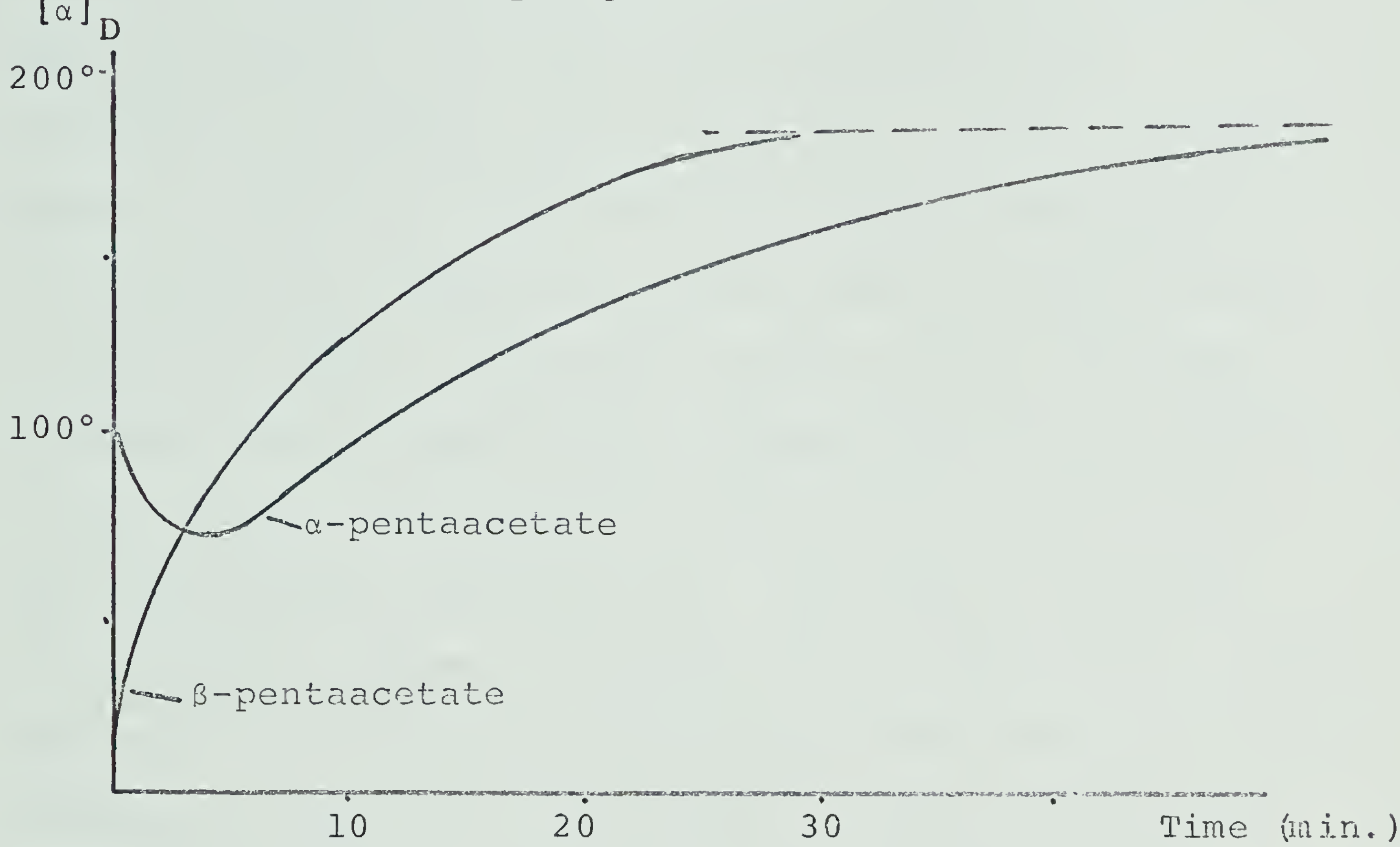


Diagram 15. Formation of alkyl 1,2-orthoesters.

The β-anomer, because of its 1,2-trans-configuration reacts readily with the added alcohol to yield the ortho-ester.

In preliminary experiments we studied the formation of glucosyl bromides to find suitable conditions for the conversion of tetra-O-acetyl-2-O-(4'-hydroxybutyryl)-α-D-glucopyranose (XVI) to tetra-O-acetyl-2-O-(4'-hydroxybutyryl)-α-D-glucopyranosyl bromide. The method most commonly employed is to treat the fully acylated sugar with a solution of hydrogen bromide in acetic acid (87). The addition of acetic anhydride to the mixture has been generally recommended (88), the reasons for its use being the possibility of obtaining a higher concentration of halogen acid and the exclusion of moisture from the mixture. In this regard we showed that the amount of added acetic anhydride has a pronounced effect on the reaction. N.m.r. evidence indicated that excess acetic anhydride results in the formation of acetyl bromide by reaction with hydrogen bromide. Thus glucosyl halide formation is markedly decreased. For example, when a 1:1 (v/v) mixture of (a) a 33% (w/w) solution of hydrogen bromide in acetic acid and (b) acetic anhydride was used, no glucosyl bromides were formed. The starting material, penta-O-acetyl-α-D-glucopyranose (XVII) was recovered unchanged.

Fig. 9. The polarimetric rates of the reaction of penta-O-acetyl-D-glucopyranoses with a 9.4% (w/v) solution of hydrogen bromide in acetic acid.



However, if a 33% (w/w) solution of hydrogen bromide in acetic acid was used the reaction was completed in less than four minutes.

The effects of the concentration of hydrogen bromide, the use of other solvents and of the addition of bromide ion in the form of tetra-n-butylammonium bromide were investigated in the case of the two anomeric penta-O-acetyl-D-glucopyranoses. The results are shown in Table II and Figs. 9, 10. It can be seen in Fig. 9 that in the reaction of penta-O-acetyl-α-D-glucopyranose (XVII) with

hydrogen bromide in acetic acid, initially the rotation decreases and then increases to reach the final value. This was thought to be due to the formation of an intermediate, possibly the β-pentaacetate or the β-bromide. However we were not able to isolate such an intermediate or to observe its presence when the reaction was performed in an n.m.r. tube. The course of the reaction could be followed well by comparing the integrations for the signals of the anomeric protons of the starting material at τ4.1 and of the final product at τ3.7. The n.m.r. spectrum did not seem to allow an argument for an intermediate, other than one with a very short existence, since the sum of the integration values for the signals of these two anomeric protons was always 1 compared to other signals in the spectrum.

The reaction of penta-O-acetyl-β-D-glucopyranose with hydrogen bromide in acetic acid to yield the α-bromide (V) could involve a straight displacement of the acetoxy group by the bromide ion. In this case no initial decrease of rotation was observed. The addition of tetra-n-butyl-ammonium bromide (1 mmole per mmole of hydrogen bromide) did not have any effect on the direction or the rate of the reaction in the case of both the α- and the β-pentaacetate.

It was then attempted to extend these experiments to

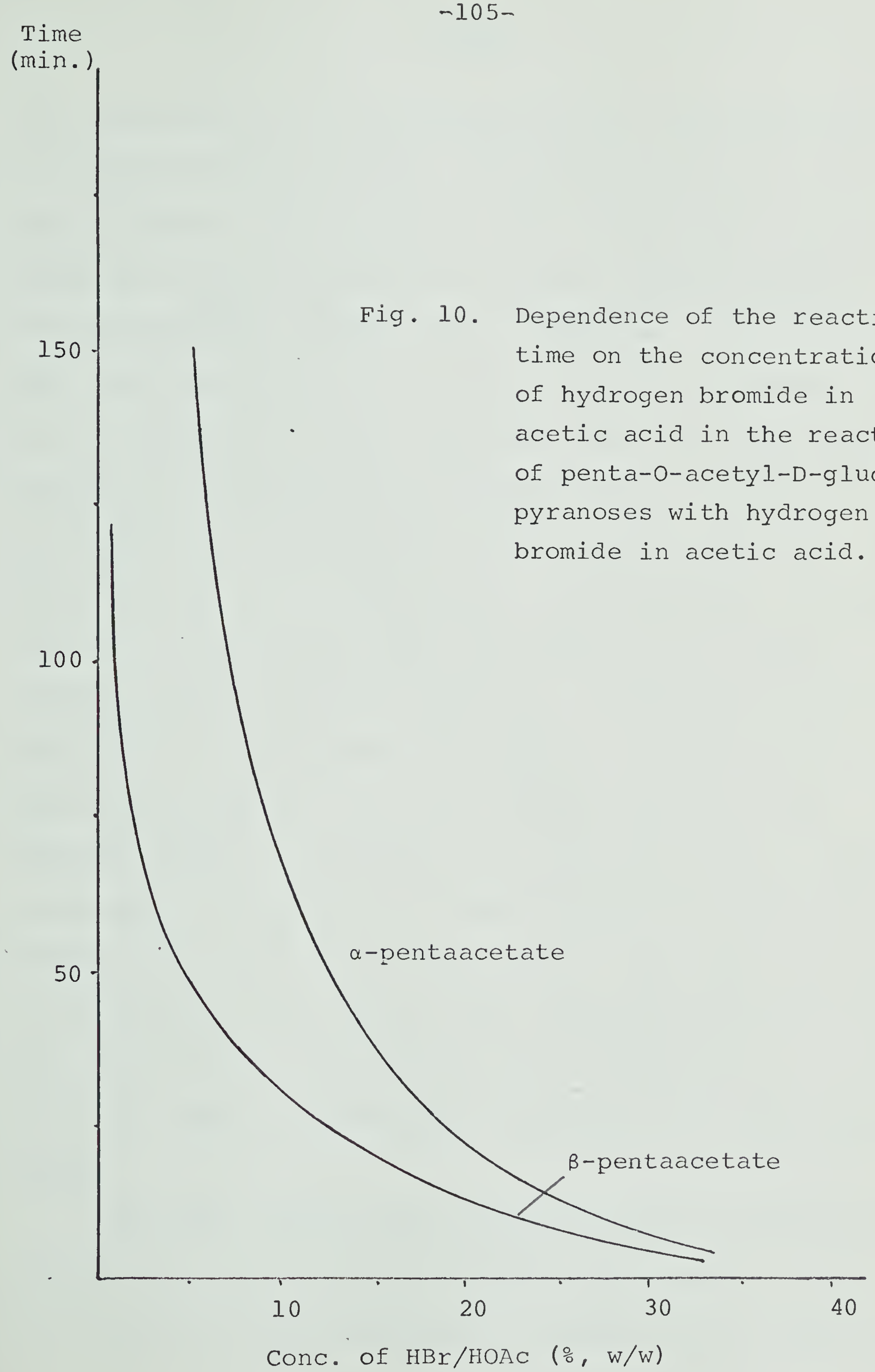


Fig. 10. Dependence of the reaction time on the concentration of hydrogen bromide in acetic acid in the reaction of penta-O-acetyl-D-glucopyranoses with hydrogen bromide in acetic acid.

the preparation of tri-O-acetyl-2-O-(4'-hydroxybutyryl)-α-D-glucopyranosyl bromide. When either XV or XVI was reacted with a cold solution (0°C) of 33% (w/w) hydrogen bromide in acetic acid for 30 minutes tetra-O-acetyl-α-D-glucopyranosyl bromide (V) was obtained. Shortening of the reaction time to 10 minutes resulted in a product the n.m.r. spectrum of which indicated about 65% 3,4,6-tri-O-acetyl-α-D-glucopyranosyl bromide (XVIII) and about 35% V, judged from the signals for the anomeric protons at τ3.45 and τ3.40 respectively. The structures of XVIII and V in this mixture were established by the use of nuclear magnetic double resonance. Irradiation at τ3.45 resulted in the collapse of a quartet at τ6.25, this indicating a proton (H-2) on a carbon bearing a free hydroxyl group. Irradiation at τ3.40 collapsed a quartet centered at τ5.15 (H-2), a signal shifted downfield by the deshielding effect of an acyl group. That this acyl group is an acetoxy group and not the 4-hydroxybutyryloxy group was indicated by the absence of the characteristic triplet at τ6.24, due to the methylene protons of the hydroxymethyl group.

For this reaction the sequence shown in Diagram 16 is proposed. In the first step the intermediate 3,4,6-tri-O-acetyl-α-D-glucopyranosyl bromide (XVIII) seems to be

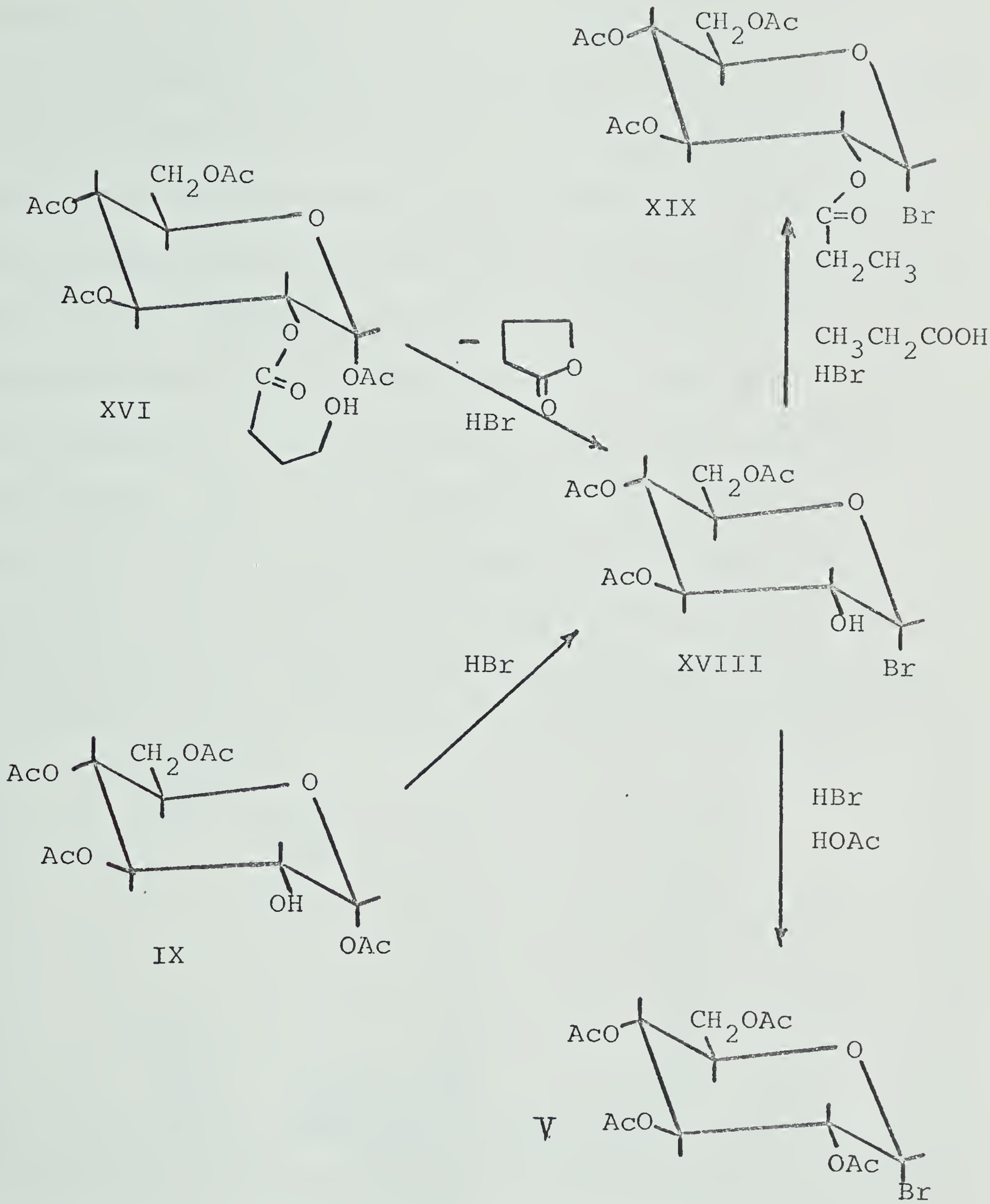


Diagram 16. Formation of fully acylated glucosyl bromides.

formed in a very fast reaction. The formation of 4-butyrolactone was indicated by n.m.r. and g. l.c. In the second step the free hydroxyl group at C-2 in XVIII is esterified in the strongly acidic medium, this reaction being slower than the first one. These suggestions were verified in experiments where 1,3,4,6-tetra-O-acetyl-α-D-glucopyranose (IX) was dissolved in a solution of 33% (w/w) hydrogen bromide in acetic acid under the same conditions. The n.m.r. spectrum of the product was virtually identical to that obtained when XVI was the starting material, with the exception of the presence of 4-butyrolactone. When a 21% (w/w) solution of hydrogen

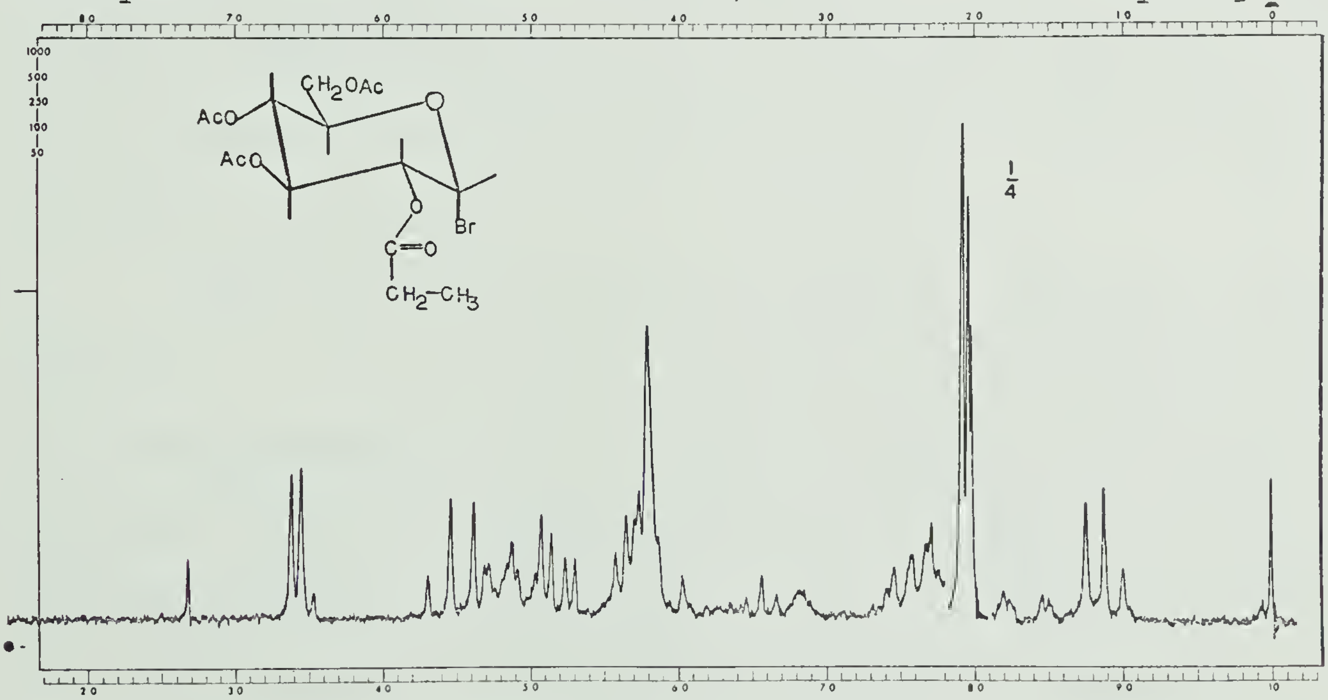


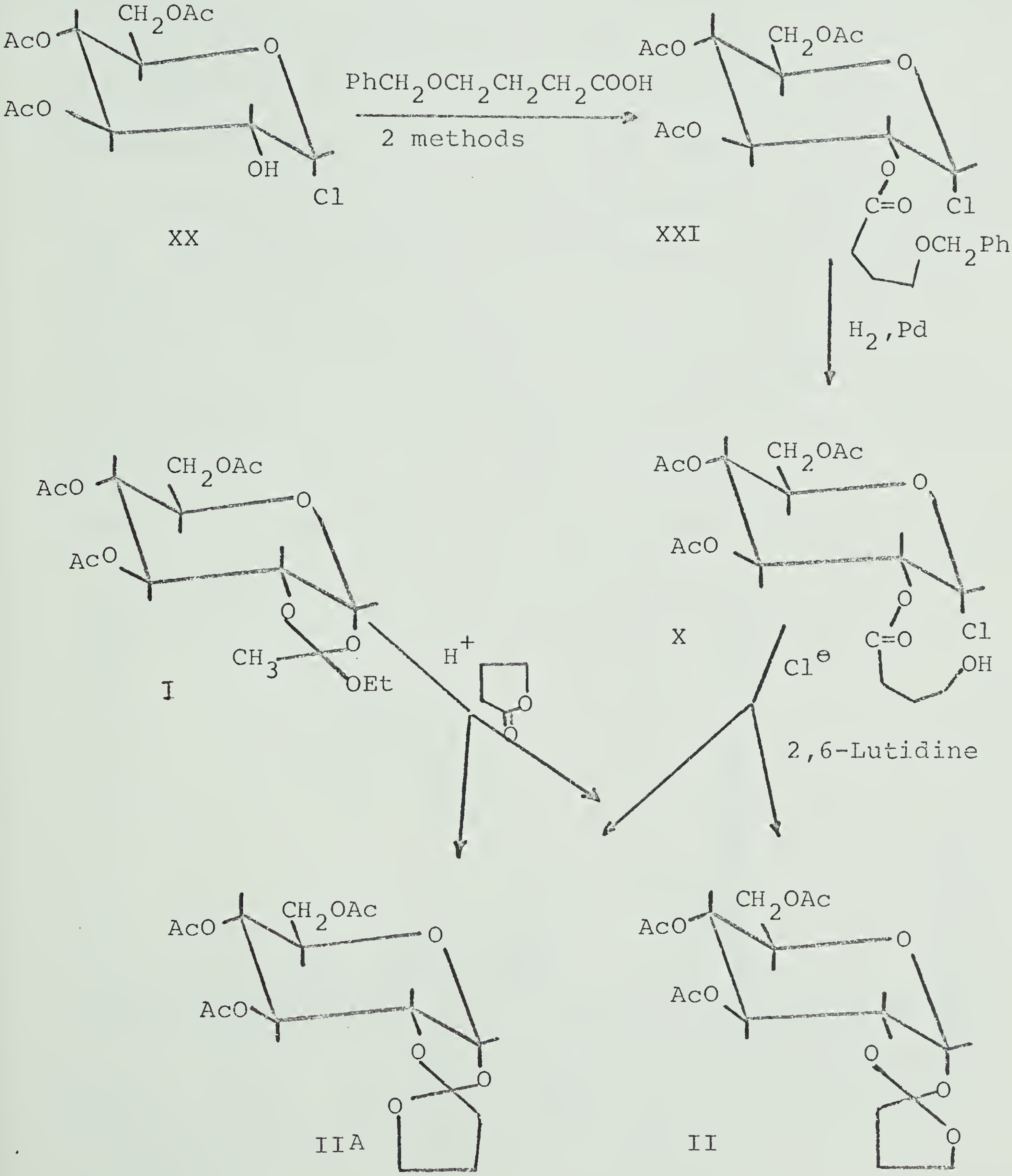
Fig. 11. N.m.r. spectrum (60 MHz) of tri-O-acetyl-2-O-propionyl-α-D-glucopyranosyl bromide (XIX) ($CDCl_3$).

bromide in propionic acid was employed the main reaction product in both cases was tri-O-acetyl-2-O-propionyl-α-D-glucopyranosyl bromide (XIX), as indicated by its n.m.r. spectrum (Fig. 11).

It was found that tetra-O-acetyl-2-O-(4'-hydroxy-butyryl)-α-D-glucopyranose (XVI) is even sensitive to acids as weak as acetic acid. XV was hydrogenated in acetic acid with palladium black as catalyst for five hours to remove the protective benzyloxy group. An n.m.r. spectrum indicated that the product consisted of about 60% XVI and about 40% 1,3,4,6-tetra-O-α-D-glucopyranose (IX), judged by the two anomeric signals and the two quartets for H-2. When the chloroform solution of this mixture was left to evaporate slowly, apparently with a trace of acetic acid still present, crystalline IX was obtained in 65% yield. Also 4-butyrolactone was detected.

Since no method could be found to introduce a bromine function at C-1 of tetra-O-acetyl-2-O-(4'-hydroxybutyryl)-α-D-glucopyranose (XVI) without destroying the acyloxy function at C-2, a new route for the preparation of the diastereoisomeric tri-O-acetyl-1,2-O-(2'-oxacyclopentylidene)-α-D-glucopyranoses (II, IIA) was devised. Diagram 17 summarizes the reaction sequence which led to the formation of these two orthoesters.

Diagram 17. Synthesis of diastereoisomeric spiro ortho-esters II, IIA.



3,4,6-Tri-O-acetyl-α-D-glucopyranosyl chloride (XX) (22, 72) was used as the starting material, this compound already having the necessary halogen function at C-1. The esterification with 4-benzyloxybutyric acid was performed analogously to the methods used in the preparation of tetra-O-acetyl-2-O-(4'-benzyloxybutyryl)-α-D-glucopyranose (XV). The two compounds, tri-O-acetyl-2-O-(4'-benzyloxybutyryl)-α-D-glucopyranosyl chloride (XXI) and tri-O-acetyl-2-O-(4'-hydroxybutyryl)-α-D-glucopyranosyl chloride (X), prepared from XXI by hydrogenation, were not obtained crystalline. Their n.m.r. spectra however show the expected features (Figs. 13, 14, Table V) and can be compared

Fig. 12. N.m.r. spectrum (60 MHz) of 3,4,6-tri-O-acetyl-α-D-glucopyranosyl chloride (XX) ($CDCl_3$).

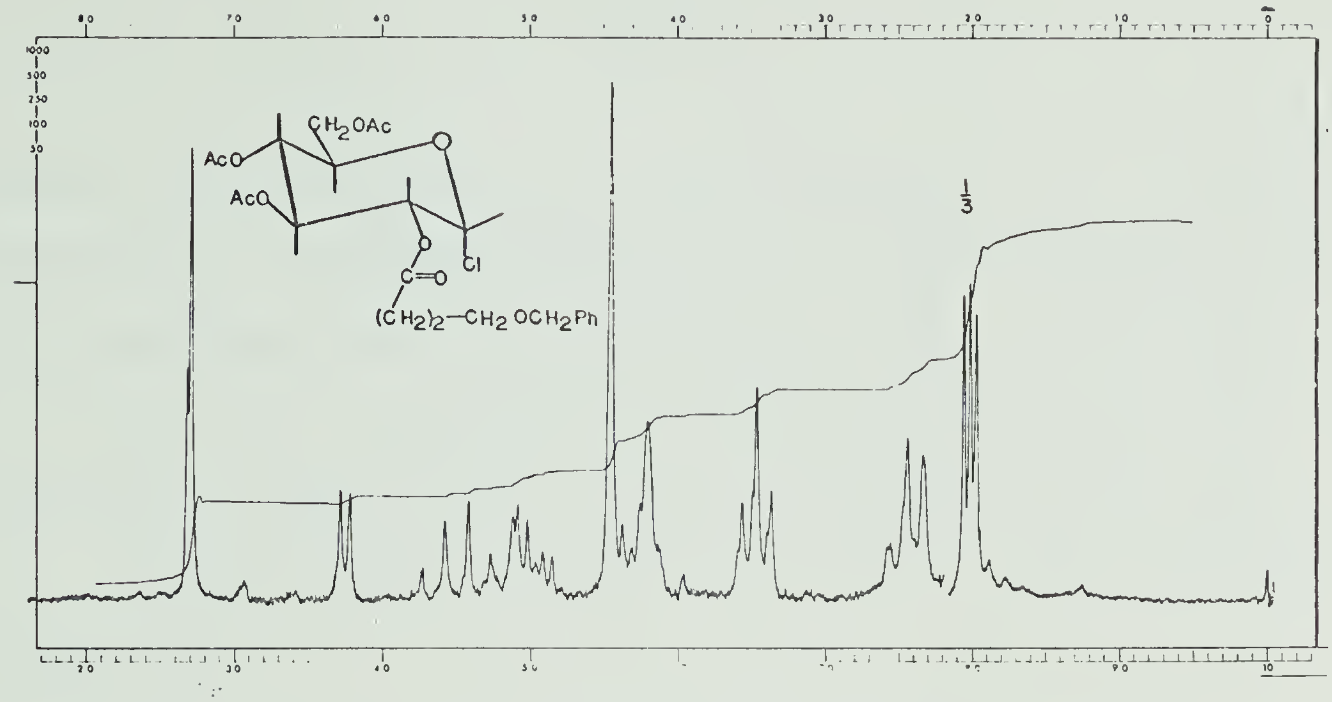


Fig. 13. N.m.r. spectrum (60 MHz) of tri-O-acetyl-2-O-(4'-benzyloxybutyryl)-α-D-glucopyranosyl chloride (XXI) ($CDCl_3$).

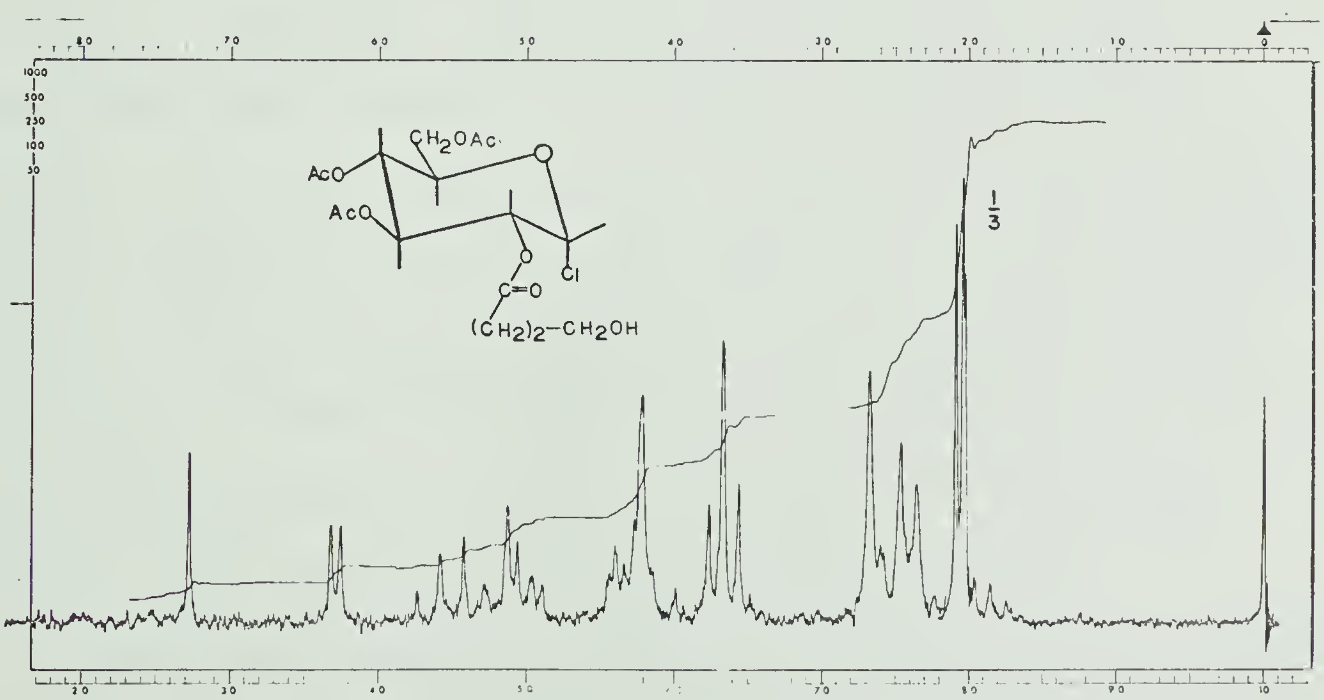


Fig. 14. N.m.r. spectrum (60 MHz) of tri-O-acetyl-2-O-(4'-hydroxybutyryl)-α-D-glucopyranosyl chloride (X) ($CDCl_3$).

readily with the spectra of tetra-O-acetyl-2-O-(4'-benzyloxybutyryl)-α-D-glucopyranose (XV) and tetra-O-acetyl-2-O-(4'-hydroxybutyryl)-α-D-glucopyranose (XVI). The quartet at τ5.02 (XXI) arises from H-2, shifted downfield by the deshielding effect of the introduced acyloxy function at C-2, compared to the corresponding signal in the starting material XX.

The preparation of the diastereoisomeric tri-O-acetyl-1,2-O-(2'-oxacyclopentylidene)-α-D-glucopyranoses (II, IIA) was achieved by reacting the α-chloride (X) with tetraethylammonium chloride in 2,6-lutidine and acetonitrile. The n.m.r. spectrum of the product (Fig. 16) confirmed that a mixture of the two isomers had been formed. The two doublets at τ4.31 and τ4.39 were assigned to the anomeric protons of the <u>exo</u> (II) and the <u>endo</u> (IIA) isomer, which was confirmed by nuclear magnetic double resonance. From the intensities of these signals it was calculated that the mixture comprises 45% of the <u>exo</u> isomer (II) and 55% of the <u>endo</u> compound (IIA).

The availability of these diastereoisomers provided a chance to study slight differences in the conformations of the pyranose ring in these compounds. It is known that <u>exo</u> alkyl 1,2-orthoesters do not have the chair conformation

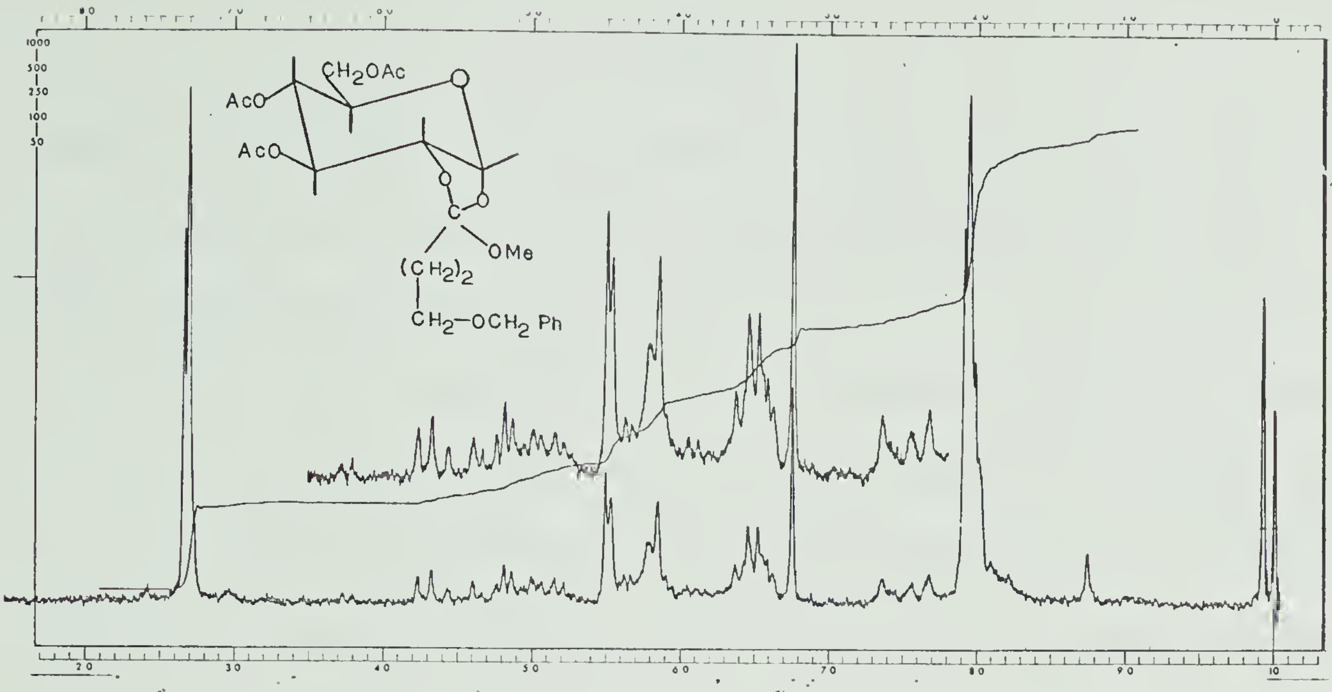


Fig. 15. N.m.r. spectrum (60 MHz) of tri-O-acetyl-1,2-O-(1'-methoxy-4'-benzyloxybutylidene)-α-D-glucopyranose (XXII) ($CDCl_3$).

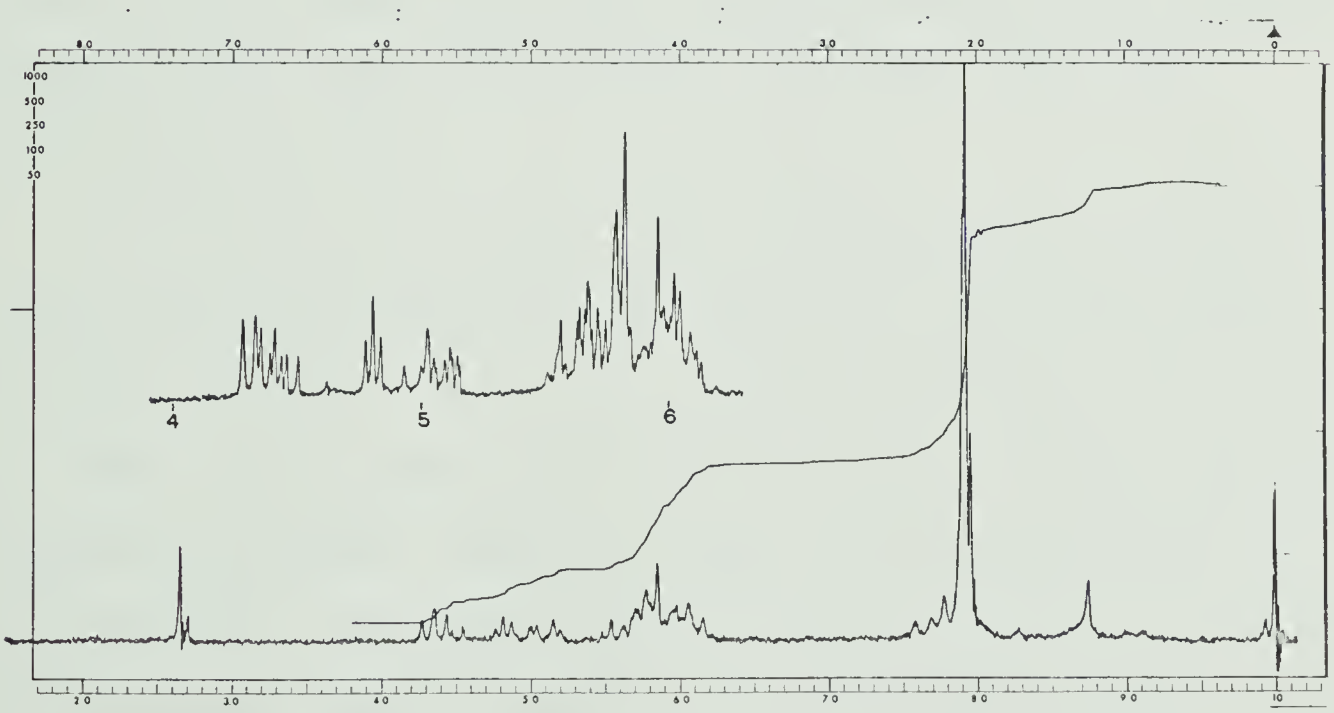


Fig. 16. N.m.r. spectrum (60 MHz) of the diastereo-isomeric tri-O-acetyl-1,2-O-(2'-oxacyclopentylidene)-α-D-glucopyranoses (II, IIA) ($CDCl_3$). Inset (100 MHz) ($CDCl_3$).

normally observed for D-glucopyranose derivatives but that these compounds have the pyranose ring distorted (7). A chair conformation would require H-2, H-3, H-4 and H-5 to occupy axial positions and to exhibit coupling constants of $J_{2,3}=J_{3,4}=J_{4,5}\sim 9$Hz. Lemieux and Morgan (7) found $J_{2,3}=J_{3,4}=2.8$ Hz and $J_{4,5}=9$ Hz and calculated that H-3 defines a dihedral angle of about 120° with both H-2 and H-4 and that H-4 and H-5 define an angle of about 180°. This indicates that some flattening of the ring must have occurred between H-1 and H-4, which is also in agreement with the value of $J_{1,2}=5.0$ Hz. A coupling constant of this magnitude has been found for similarly positioned bridgehead protons (47) and reflects a dihedral angle of approximately 40°.

In contrast to this Coxon and Hall (62) proposed a skew boat conformation for a series of 1,2-O-alkylidene derivatives which gave n.m.r. spectra virtually identical to those of the <u>exo</u> alkyl 1,2-orthoesters. These workers suggested dihedral angles of about 42° between H-1, H-2, H-3 and H-4. Since the Karplus equation, used to calculate the dihedral angles, involves a $\cos^2$ term two angles may be calculated for each coupling constant.

Recently an X-ray crystal structure investigation of 1,2-O-aminoisopropylidene-α-D-glucopyranose hydroiodide,

a compound very similar in structure to the discussed 1,2-orthoesters and 1,2-ketals, was performed. Trotter and Fawcett (89) were able to deduce that the pyranose ring does not have the skew boat conformation suggested by Coxon and Hall (62) but rather a flattened chair conformation. The five-membered dioxolane ring has an envelope conformation with the dioxolane 2-carbon atom displaced only 0.36Å from the plane of the other four atoms. The authors realized that there might be small differences between the conformations of the pyranose ring of a sugar in solution and of a crystalline derivative.

We found that the n.m.r. parameters (Table VII) of the pyranose ring protons of tri-O-acetyl-1,2-O-(2'-exo-oxacyclopentylidene)-α-D-glucopyranose (II) are virtually identical to those of exo alkyl 1,2-orthoesters (7) and 1,2-O-alkylidene derivatives (62). The observed coupling constants $J_{1,2}$=5.0 Hz, $J_{2,3}$=$J_{3,4}$=3.0 Hz and $J_{4,5}$=9 Hz indicate that the spiro-attachment of the additional five-membered ring does not have an appreciable effect on the conformation of either the pyranose or the dioxolane ring. These results are supported by our investigations of the 1,2-O-alkylidene derivatives discussed later.

However, the n.m.r. spectrum of tri-O-acetyl-1,2-O-(2'-endo-oxacyclopentylidene)-α-D-glucopyranose (IIA) shows

Table VII. N.m.r. parameters of 3,4,6-tri-O-acetyl-α-D-glucopyranose 1,2-O-derivatives.

	H-1 (τ)	$J_{1,2}$ (Hz)	H-2 (τ)	$J_{2,3}$ (Hz)	H-3 (τ)	$J_{3,4}$ (Hz)	H-4 (τ)	$J_{4,5}$ (Hz)
(I)(1'-*exo*-ethoxyethylidene)[a]	4.30	5.0	5.78	3.0	4.82	3.0	5.10	9.0
(IA)(1'-*endo*-ethoxyethylidene)[a]	4.33	5.5	-	4.5	4.46	7.4	-	-
(XXIX)(1'-*exo*-n-propyloxyethylidene)[a]	4.27	5.0	-	3.0	4.79	3.0	5.07	9.0
(XI)(1'-benzyloxyethylidene)[a]	4.32	5.0	-	3.0	4.80	3.0	5.09	9.0
(II)(2'-*exo*-oxacyclopentylidene)[b]	4.31	5.0	5.65	3.0	4.81	3.0	5.09	9.0
(IIA)(2'-*endo*-oxacyclopentylidene)[b]	4.39	5.5	5.75	4.7	4.44	7.0	5.01	9.5

a. 60 MHz, $CDCl_3$.
b. 100 MHz, $CDCl_3$.

Table VIII. Dihedral angles, calculated for diastereoisomeric 1,2-orthoesters of D-glucopyranose (II, II A) and D-galactopyranose (XLII)

	H-1/H-2		H-2/H-3		H-3/H-4		H-4/H-5	
	J (Hz)	Θ	J (Hz)	Θ	J (Hz)	Θ	J (Hz)	Θ
<u>exo</u> (II)	5.0	41°	3.0	124°	3.0	124	9.0	∿180°
<u>endo</u> (IIA)	5.5	38°	4.7	135°	7.0	147	9.5	∿180°
<u>exo</u> (XLII)	5.0	41°	6.5	145°	3.5	50°	2.5	55°

that compounds of this type differ slightly in conformation when compared with those of the <u>exo</u> type. From the observed coupling constants the dihedral angles listed in Table VIII were calculated. A significant downfield shift by ∿0.4 ppm was observed for the resonance signal of H-3. The position of H-3 at τ4.44 was verified by nuclear magnetic double resonance. Irradiation at τ4.39 (H-1) collapsed a multiplet at τ5.75 (H-2). Subsequent irradiation of H-2 changed the quartet at τ4.44 (H-3) into a doublet with spacing 7.0 Hz ($J_{3,4}$) and the doublet at τ4.39 (H-1) into a single line. The unusual downfield shift of H-3 can be explained in terms of the close proximity of H-3 to the oxygen atom of the oxacyclopentylidene ring.

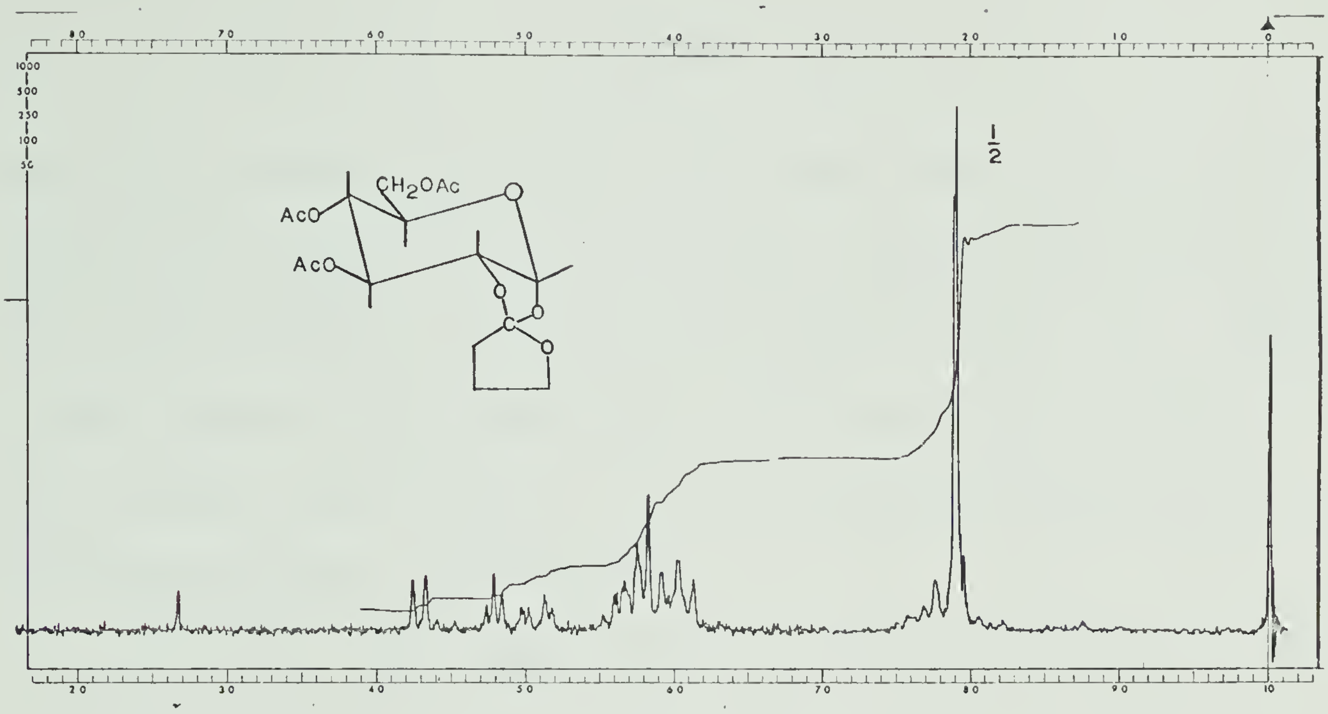


Fig. 17. N.m.r. spectrum (60 MHz) of tri-0-acetyl-1,2-0-(2'-exo-oxacyclopentylidene)-α-D-glucopyranose (II) ($CDCl_3$).

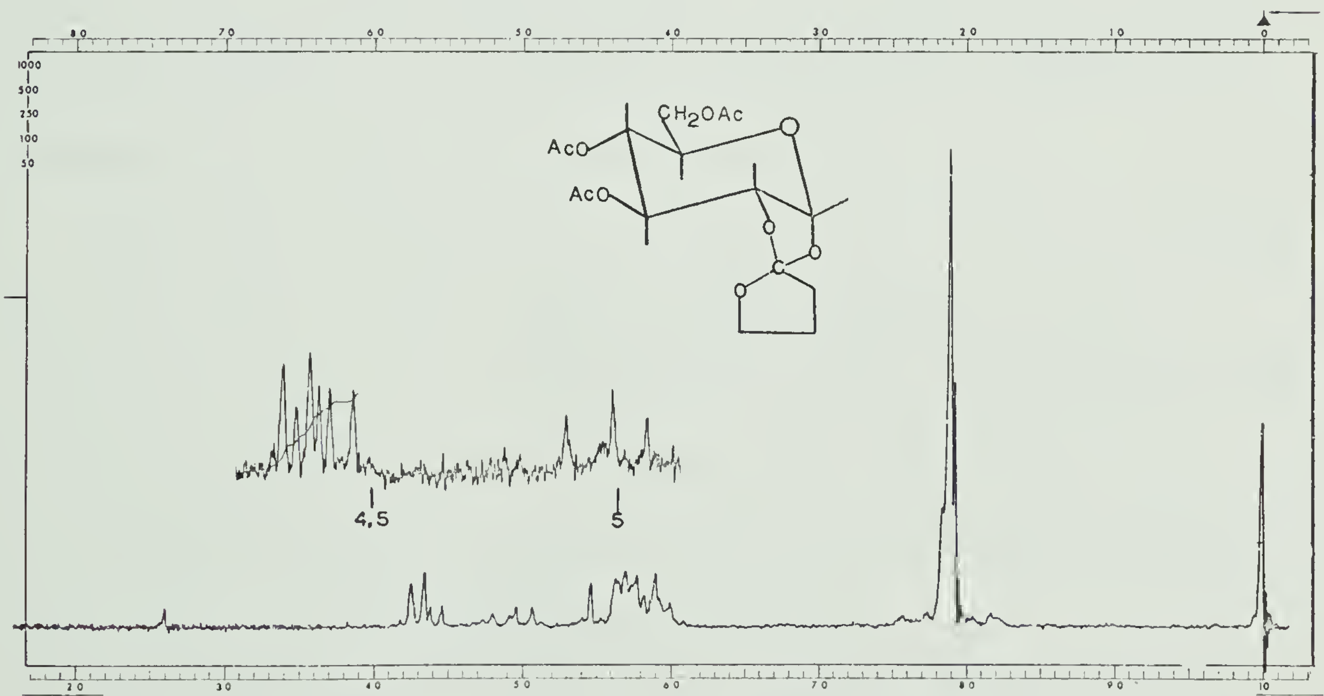


Fig. 18. N.m.r. spectrum (60 MHz) of tri-0-acetyl-1,2-0-(2'-endo-oxacyclopentylidene)-α-D-glucopyranose (IIA) ($CDCl_3$). Inset (100 MHz) ($CDCl_3$).

Molecular models indicated that this close proximity can only be obtained if both dihedral angles between H-2 and H-3 and between H-3 and H-4 are greater than 90°. These facts support the suggestions by Lemieux and Morgan (7) and Trotter and Fawcett (89) of a slightly distorted, flattened chair conformation.

However, the suggestion of the latter workers, that the four atoms C-1, C-2, O-1, O-2 occupy one plane, disagrees with the observed coupling constant $J_{1,2}$∿5 Hz for compounds of this type. Also, molecular models indicated that a close proximity between H-3 and the oxygen atom of the oxacyclopentylidene ring cannot be obtained if the dioxolane ring adopts the envelope conformation suggested by Trotter and Fawcett (89).

The small differences in the values of $J_{1,2}$ of the exo (5.0 Hz) and the endo (5.5 Hz) isomer do not necessarily reflect a difference in the conformation of the dioxolane ring. It is known (53, 54, 90) that this could be due to small differences in the electronegativity of the neighbouring groups.

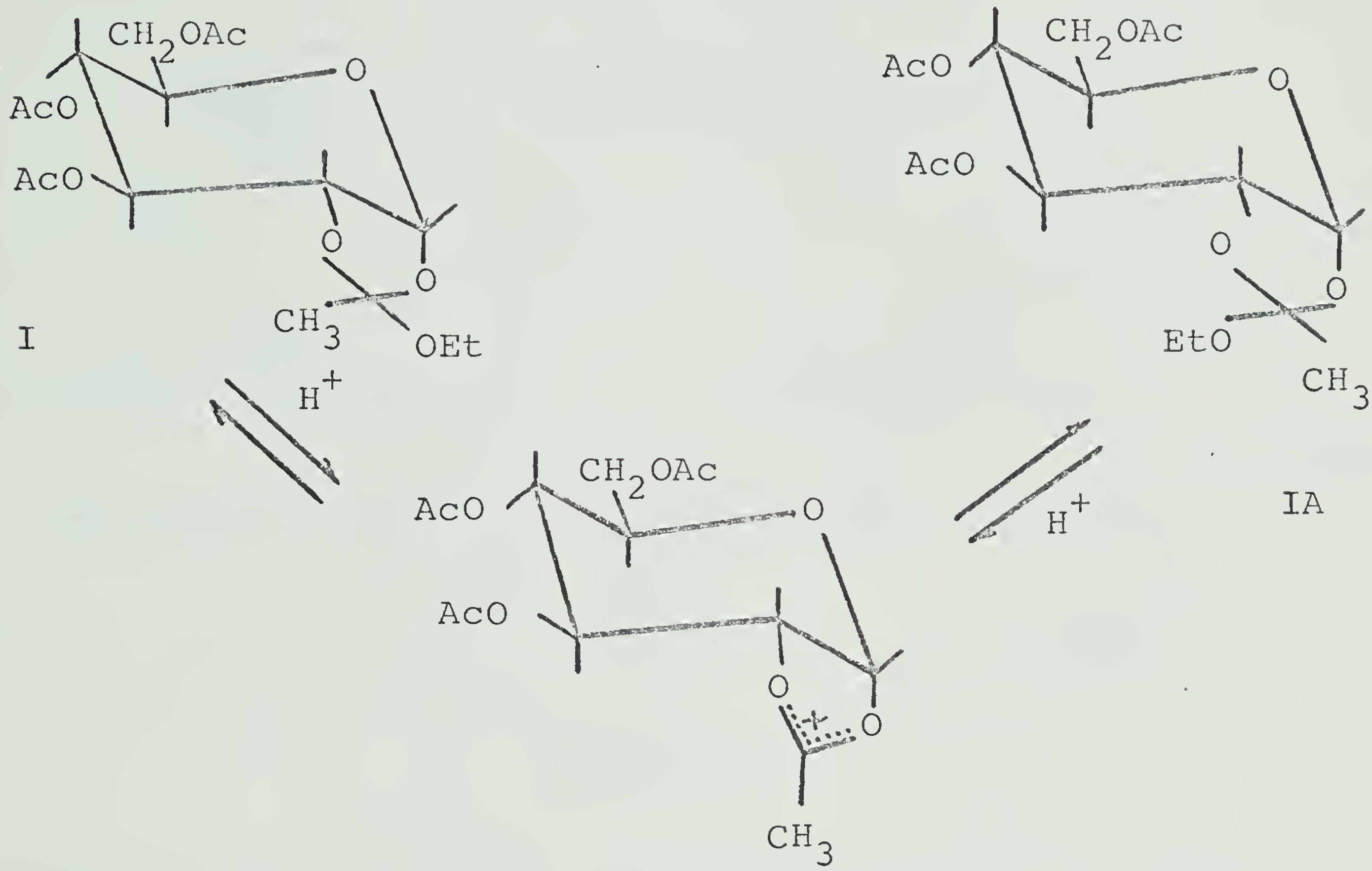
The differences which were observed in the n.m.r. spectra of the diastereoisomeric spiro orthoesters (II, IIA) were also apparent in the case of the diastereoisomeric tri-O-acetyl-1,2-O-(1'-ethoxyethylidene)-α-D-

glucopyranoses (I,IA). A mixture of these two compounds was obtained by acid catalyzed equilibration of the pure tri-O-acetyl-1,2-O-(1'-exo-ethoxyethylidene)-α-D-glucopyranose (I) (Diagram 18). Again a downfield shift of ∿0.4 ppm was observed for the resonance signal of H-3 in the endo isomer when compared to the exo compound (Table VII).

At this point it appears to be interesting to discuss a reaction which was developed to synthesize 1,2-O-alkylidene-α-D-glucopyranoses, thus making this class of compounds easily accessible (Diagrams 19, 20). This reaction could be extended to the synthesis of the tri-O-acetyl-1,2-O-(2'-oxacyclopentylidene)-α-D-glucopyranoses (II, IIA), prepared before by the more lengthy route described in Diagram 17.

The preparation of the 1,2-ketals involved the reaction of tri-O-acetyl-1,2-O-(1'-exo-ethoxyethylidene)-α-D-glucopyranose (I) with a ketone and p-toluenesulfonic acid as catalyst as outlined in Diagrams 19, 20. Strictly anhydrous conditions must be used since trace amounts of water would result in the formation of 1,3,4,6-tetra-O-acetyl-α-D-glucopyranose (IX), thus diminishing the yield of the 1,2-ketal. Therefore the technique shown in Diagram 19 was devised to ensure a dry reaction medium. Trimethyl

Diag. 18. Diasteroisomeric tri-0-acetyl-1,2-0-(1'-ethoxyethylidene)-α-D-glucopyranoses (I, IA).



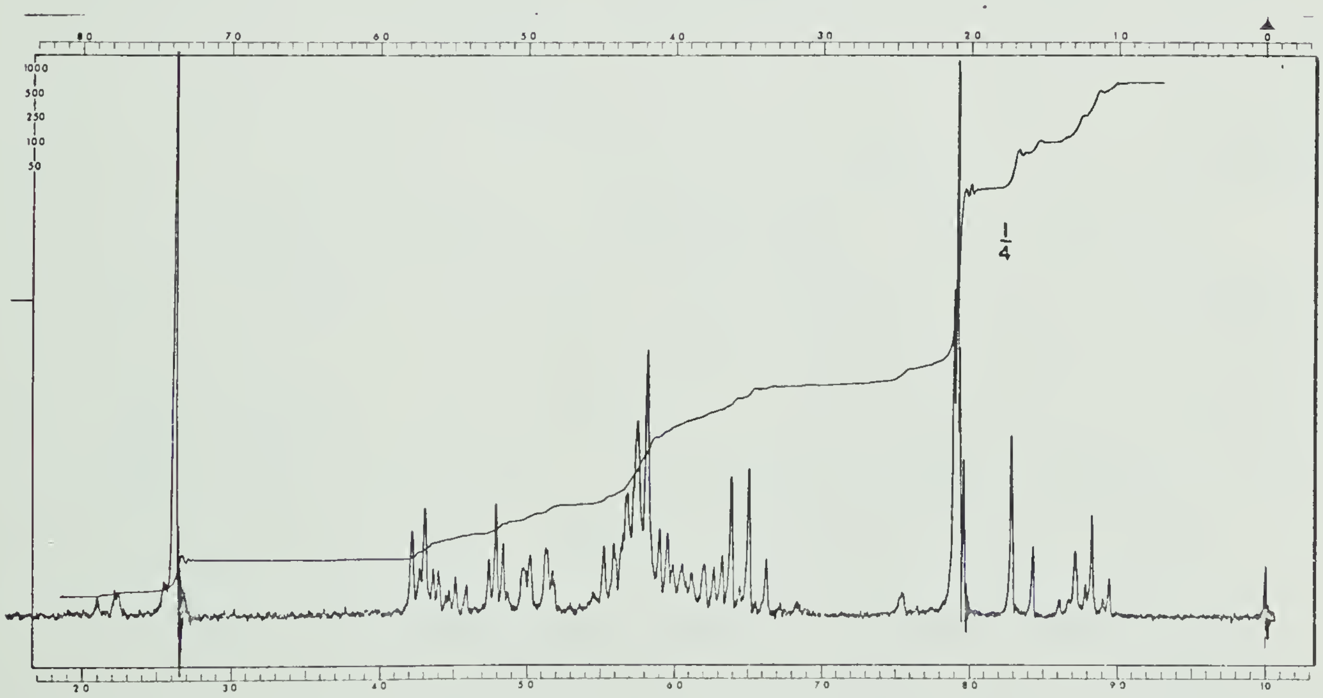


Fig. 19. N.m.r. spectrum (60 MHz) of the diastereo-isomeric tri-0-acetyl-1,2-0-(1'-ethoxyethylidene)-α-D-glucopyranoses (I, IA) ($CDCl_3$).

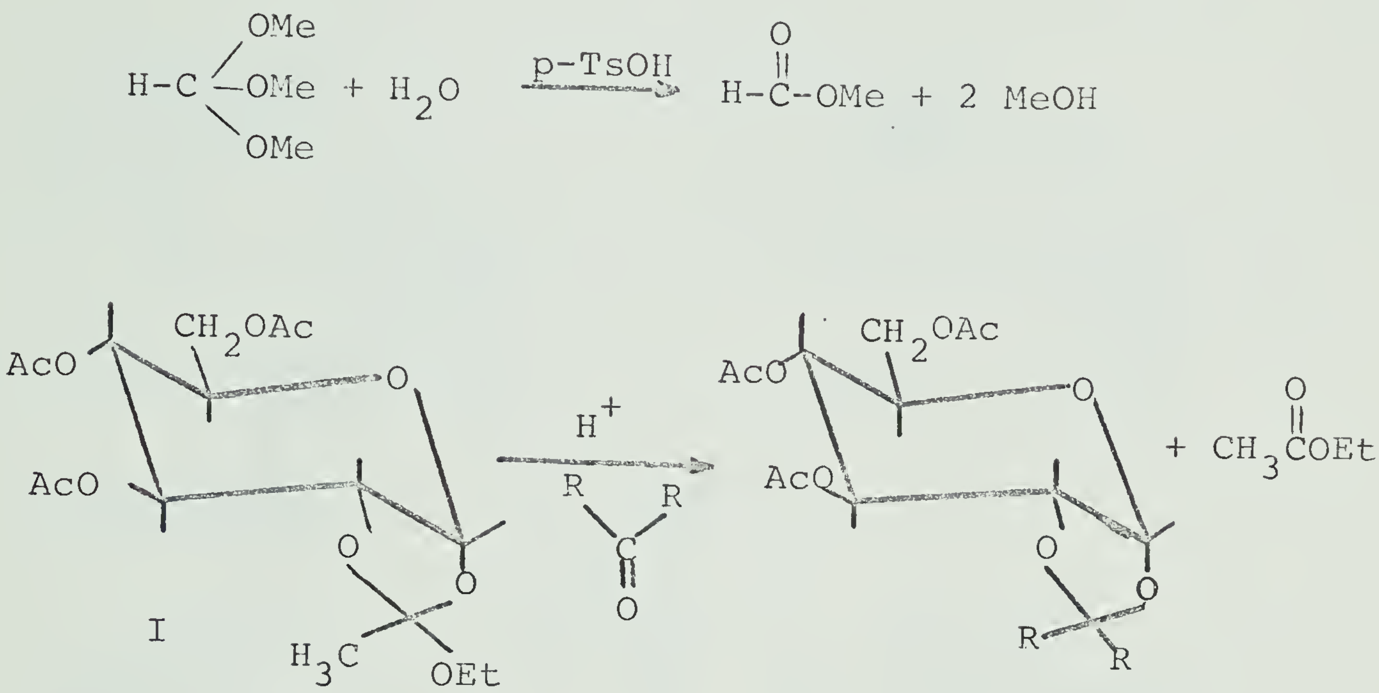
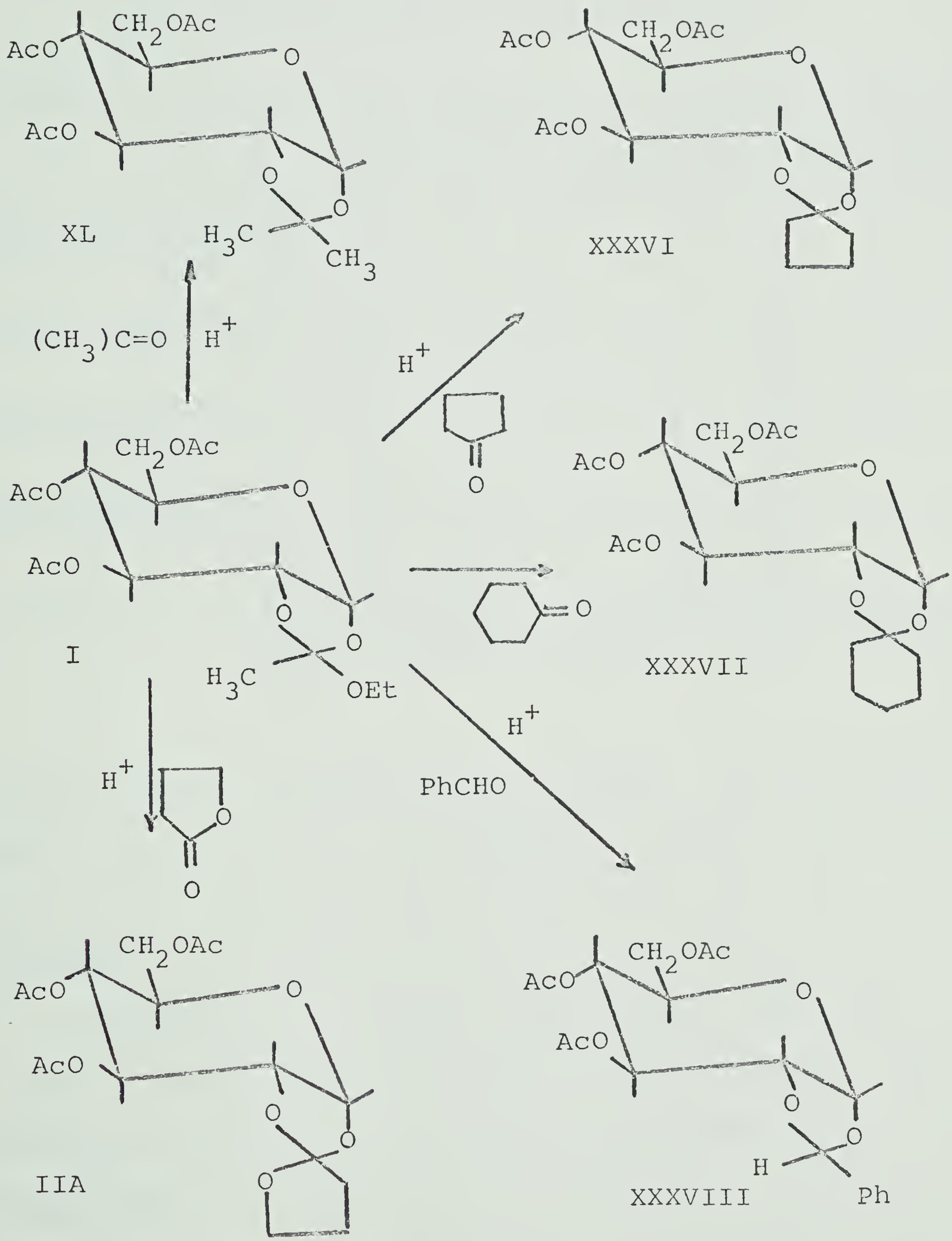


Diagram 19.

orthoformate (0.1 mole) was added to the ketone (1.0 mole) and then p-toluenesulfonic acid. The solution was kept for 10 minutes to ensure hydrolysis of the orthoester by the water present in the mixture. The volatile reaction products methanol and methyl formate, formed in the hydrolysis, were removed by subjecting the system to a vacuum for 10 minutes. Subsequently the glucose 1,2-orthoester was added. This technique proved to be very efficient since nearly quantitative yields were obtained in the case of the cyclopentylidene, cyclohexylidene and benzylidene derivatives. In the preparation of tri-O-acetyl-1,2-O-isopropylidene-α-D-glucopyranose (XL) 2,2-dimethoxypropane was used as the drying agent. Examination



Diag. 20. Exchange reactions of tri-O-acetyl-1,2-O-(1'-exo-ethoxyethylidene)-α-D-glucopyranose (I).

Table IX. N.m.r. parameters of 3,4,6-tri-O-acetyl-α-D-glucopyranose 1,2-O-derivatives.

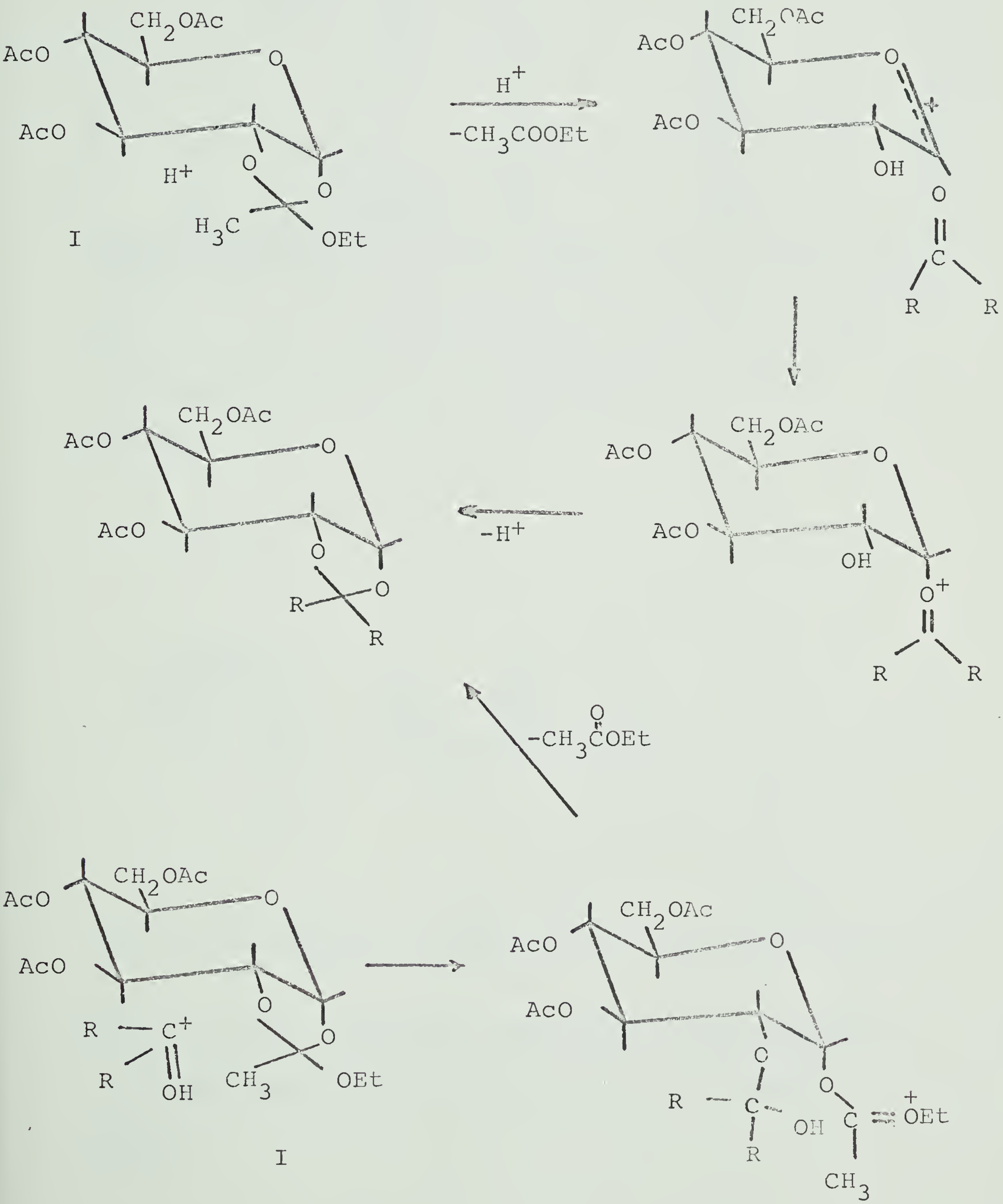
	H-1 (τ)	$J_{1,2}$ (Hz)	H-3 (τ)	$J_{2,3}$ (Hz)	H-4 (τ)	$J_{3,4}$ (Hz)	$J_{4,5}$ (Hz)
isopropylidene (XL)	4.34	5.0	4.73	3.0	5.05	3.0	9.0
cyclopentylidene (XXXVI)	4.45	5.0	4.78	3.0	5.08	3.0	9.0
cyclohexylidene (XXXVII)	4.34	5.0	4.72	3.0	5.05	3.0	9.0
exo-benzylidene (XXXVIII)	4.23	5.0	4.68	3.0	5.05	3.0	9.0

Spectra taken at 60 MHz in $CDCl_3$ solution.

of the volatile products of the reactions described above showed the presence of ethyl acetate. Keeping this in mind, two possible mechanisms for the reaction of a 1,2-orthoester with a ketone can be envisaged (Diagram 21).

From the n.m.r. spectra (Figs. 20-23, Table IX) of the 1,2-ketals described here it is obvious that the conformations of these compounds are very similar to those of *exo* alkyl 1,2-orthoesters (7) and other 1,2-O-alkylidene derivatives (42, 62). Assignments of the signals in the n.m.r. spectra were confirmed by nuclear magnetic double resonance experiments.

Diag. 21. Mechanisms for the formation of 1,2-alkylidene derivatives of D-glucopyranose.



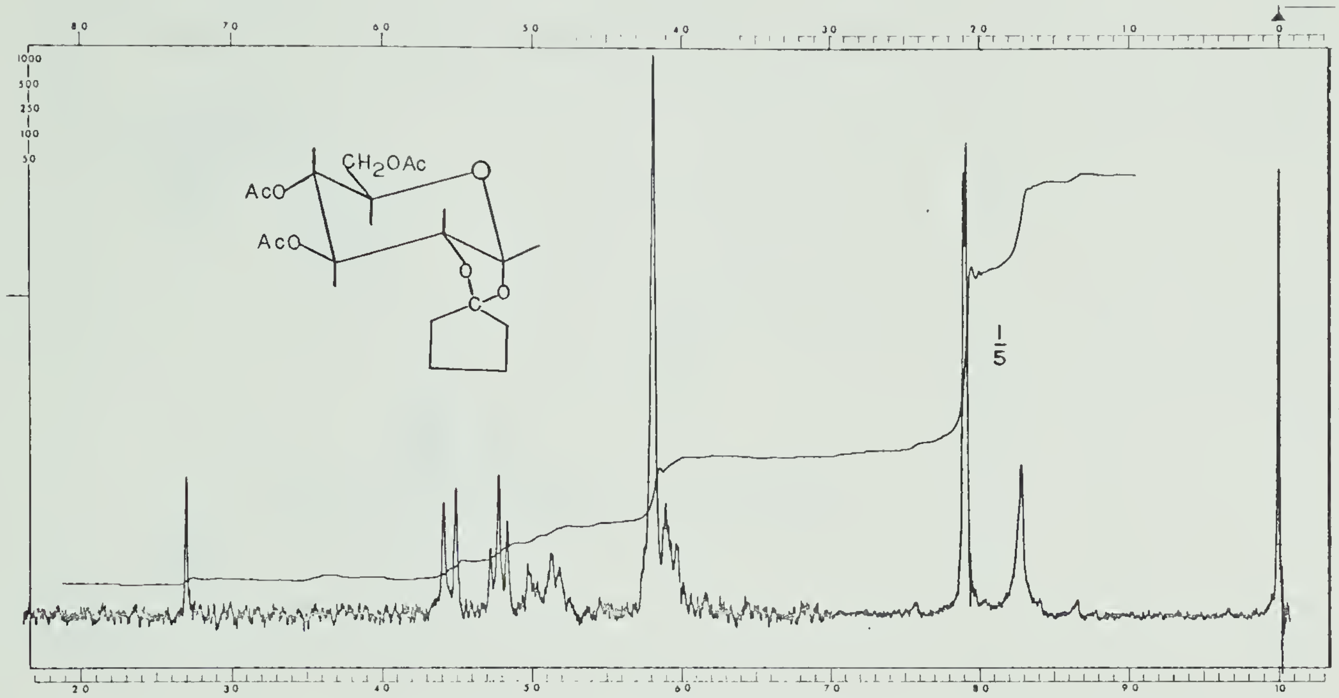


Fig. 20. N.m.r. spectrum (60 MHz) of tri-0-acetyl-1,2-0-cyclopentylidene-α-D-glucopyranose (XXXVI) ($CDCl_3$).

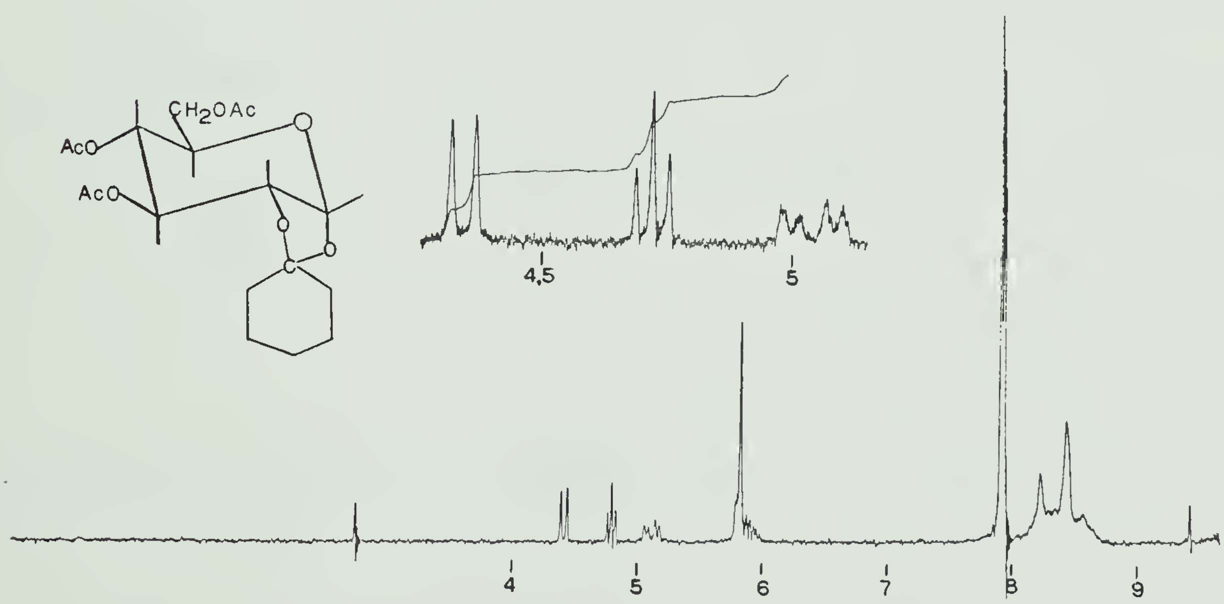


Fig. 21. N.m.r. spectrum (100 MHz) of tri-0-acetyl-1,2-0-cyclohexylidene-α-D-glucopyranose (XXXVII) ($CDCl_3$).

Fig. 22. N.m.r. spectrum (60 MHz) of the diastereoisomeric tri-0-acetyl-1,2-0-benzylidene-α-D-glucopyranoses (XXXVIII, XXXVIIIA) ($CDCl_3$).

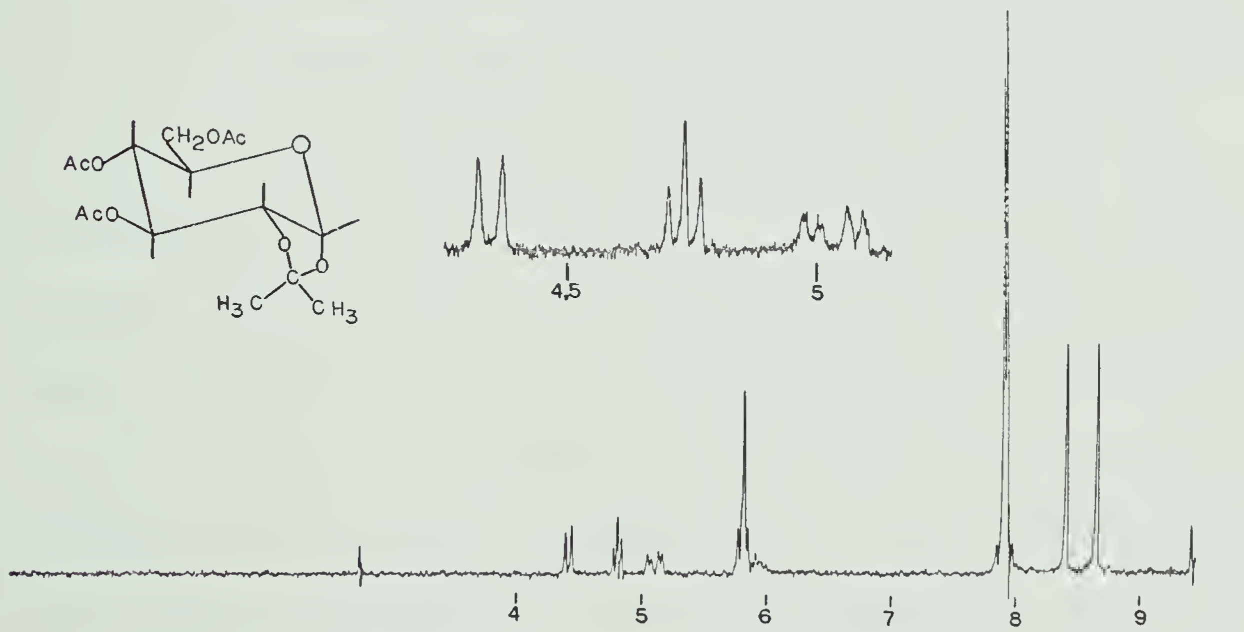


Fig. 23. N.m.r. spectrum (100 MH_z) of tri-0-acetyl-1,2-isopropylidene-α-D-glucopyranose (XL) ($CDCl_3$).

It is of interest to note that in the case of the 1,2-O-benzylidene compound previously only one of the two diastereoisomers has been isolated (39, 42). Fletcher and coworkers (39) obtained tri-O-acetyl-1,2-O-benzylidene-α-D-glucopyranose as a minor component in the acid catalyzed condensation of D-glucose with benzaldehyde. The approach of Rees and coworkers (42) involved the reaction of tri-O-acetyl-1,2-O-isopropylidene-α-D-glucopyranose with benzaldehyde and sulfuric acid. The physical constants obtained by Fletcher (39) and Rees (42) indicated that they had prepared the same isomer. The n.m.r. spectrum of the product obtained in our preparation showed that both isomers (Diagram 22) were present in the mixture in a ratio of about 3:1, judged by the integrations for the signals of the benzylidene acetal hydrogen atom. A comparison of our n.m.r. data with those from the literature is shown in Table X. It can be seen that the isomer described in the literature previously was obtained as the minor component. It also was apparent that the isomer, obtained as the major component, has virtually the same n.m.r. parameters as those exhibited by the exo alkyl 1,2-orthoesters of glucose (7) and the 1,2-O-alkylidene derivatives (42, 62). On the other hand slightly different coupling constants $J_{2,3}$ and $J_{3,4}$ were observed for the

other isomer. These deviations can be visualized as the result of extensive interactions between the phenyl group and H-3 and H-5 as was detected by the use of molecular models. This indicates that the latter compound is in fact the endo isomer (XXXVIIIA) and that the isomer obtained as the major component is the exo derivative (XXXVIII). Interactions of this type have been observed previously by Lemieux and Morgan (7) in the case of tri-O-acetyl-1,2-O-(1'-exo-methoxy-2',2'-dimethylpropylidene)-α-D-glucopyranose. The presence of the endo t-butyl group resulted in a decrease of the dihedral angle between H-4 and H-5 and an increase of that defined by H-3 and H-4.

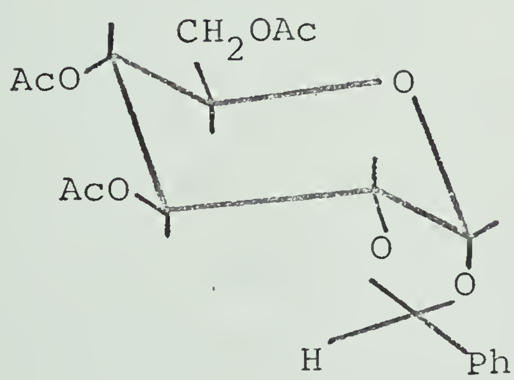
A substantial difference of 0.58 ppm was observed for the chemical shifts of the benzylidene protons in the diastereoisomeric 1,2-O-benzylidene derivatives. The position of the signal of this proton in the exo isomer (τ4.13) was found to be virtually identical to the signal of the analogous proton in 2-phenyl-1,3-dioxolane (τ4.10), which is expected. On the other hand the n.m.r. spectrum of the endo isomer exhibited a signal at τ3.56.

As was mentioned before, the new reaction developed for the preparation of cyclic ketals proved to be a convenient method for the synthesis of the diastereoisomeric tri-O-acetyl-1,2-O-(2'-oxacyclopentylidene)-α-D-gluco-

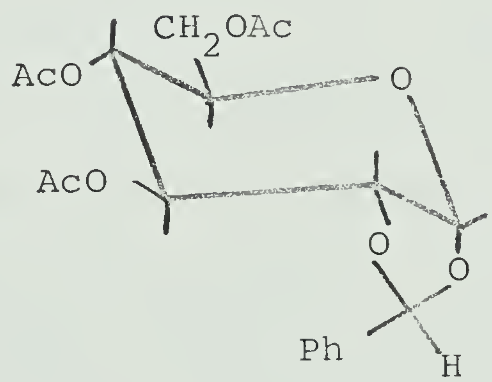
Table X. N.m.r. parameters of 1,2-benzylidene derivatives of D-glucopyranose. Comparison of literature values with data obtained by author.

	H-1 (τ)	$J_{1,2}$ (Hz)	H-3 (τ)	$J_{2,3}$ (Hz)	$J_{3,4}$ (Hz)	H-4 (τ)	acetal H(τ)
Coxon(62)	4.29	4.0	4.67	4.0	4.0	5.03	3.59
Rees(42)	4.25	4.8	4.63	4.6	4.6	5.01	-
XXXVIII	4.26	5.0	4.70	3.0	3.0	5.06	4.13
XXXVIIIA	4.26	5.0	4.65	4.5	4.5	5.02	3.56

Spectra taken at 60 MHz in $CDCl_3$ solution.



XXXVIII (exo)



XXXVIIIA (endo)

Diagram 22

pyranoses (II, IIA). 4-Butyrolactone was employed instead of a ketone to yield a mixture in which the exo isomer predominated slightly (55%). The n.m.r. spectra and physical constants of the products obtained in this case were identical to those obtained from the materials prepared according to the more lengthy reaction sequence described in Fig. 17.

The research conducted by Lemieux and Morgan (6,8) to investigate the suitability of glucose alkyl 1,2-orthoesters for the synthesis of α-D-glucopyranosides involved the reaction of a 1,2-orthoester with an alcohol and an acidic catalyst. When the addition of the alcohol was omitted very little glucoside was formed. The conclusion was that the free alcohol gives rise to the formation of the glucoside and that a rearrangement of the orthoester does not take place. Lemieux and Morgan (6, 8) employed p-toluenesulfonic acid or picric acid in methylene chloride as the reaction media and found that the 2-acetoxy group had been removed completely from the products. The major components were the α- and β-alkyl 3,4,6-tri-O-acetyl-α-D-glucopyranosides with the α-anomer predominating.

In our work, to examine the utility of the diastereoisomeric tri-O-acetyl-1,2-O-(2'-oxacyclopentylidene)-α-D-glucopyranoses (II, IIA) for the synthesis of glucosides,

we followed the analytical procedure used by Lemieux and Morgan (8). These workers employed g. l.c. analysis for the investigation of the trimethylsilyl derivatives of the reaction products. In preliminary experiments known quantities of pentaerythritol tetraacetate, chosen as internal standard, were added to known quantities of authentic methyl, ethyl, isopropyl, and t-butyl α- and β-D-glucopyranoside tetraacetates and penta-O-acetyl-α-D-glucopyranose and deacetylated with triethylamine methanol-water. Subsequently the trimethylsilyl derivatives were formed (65) and the methylene chloride solutions of these derivatives were analyzed by g. l.c. In this way the correlation of the integrations for the sugar and the pentaerythritol tms derivatives could be determined.

The effects of different column packings and different temperatures were studied and it was found that a column packed with 3% SE-30 on Chromosorb W produced optimum conditions for the present purpose. Our results indicated that the α-D-glucosides always preceded the β-isomers, that the retention times of the α-D-glucosides differed only slightly for different aglycons but the difference was much more pronounced for the β-anomers. The tms derivative of α-D-glucose had the same retention time as those of the α-D-glucosides, β-D-glucose however had a

longer retention time than the β-D-glucosides under investigation. Since the reaction of the orthoester with an alcohol and an acidic catalyst always produced small amounts of compounds which were deacetylated to give α- and β-D-glucose, it was necessary to calculate the integration value for α-D-glucose from that of the β-anomer. This was possible because the ratio of α- to β-D-glucose was constant under the standard deacetylation conditions employed. Hence the yields of α-D-glucoside and glucose could still be determined, despite the fact that their peaks coincided. The small amounts of D-glucose which were present in the deacetylated mixture could be due to trace amounts of water in the reaction medium or to unreacted orthoester. We found that tri-O-acetyl-1,2-O-(2'-oxacyclopentylidene)-α-D-glucopyranose (II, IIA) was hydrolyzed by aqueous acid to yield 3,4,6-tri-O-acetyl-D-glucopyranose. Hence this would have been the product if unreacted orthoester was subjected to the deacetylation procedure, since the reaction mixture was first dissolved in methanol-water.

In preliminary experiments we found that the use of p-toluenesulfonic acid as the catalyst resulted to a small extent in the formation of sugar tosylates as was seen in the n.m.r. spectra of the crude reaction products. The yields of glucosides were rather poor compared to the

results we obtained with antimony pentachloride (Table III). It was found that under the conditions employed exo and endo tri-O-acetyl-1,2-O-(2'-oxacyclopentylidene)-α-D-glucopyranose (II, IIA) gave identical results. A mixture of these two compounds was therefore used in the reactions described below.

Three 1,2-orthoesters, tri-O-acetyl-1,2-O-(2'-oxacyclopentylidene)-α-D-glucopyranose (II, IIA), tri-O-acetyl-1,2-O-(1'-exo-ethoxyethylidene)-α-D-glucopyranose (I) and tri-O-acetyl-1,2-O-(1'-exo-n-propyloxyethylidene)-α-D-glucopyranose (XXIX) were reacted under standard conditions in methylene chloride as the solvent with an alcohol and antimony pentachloride. The products and

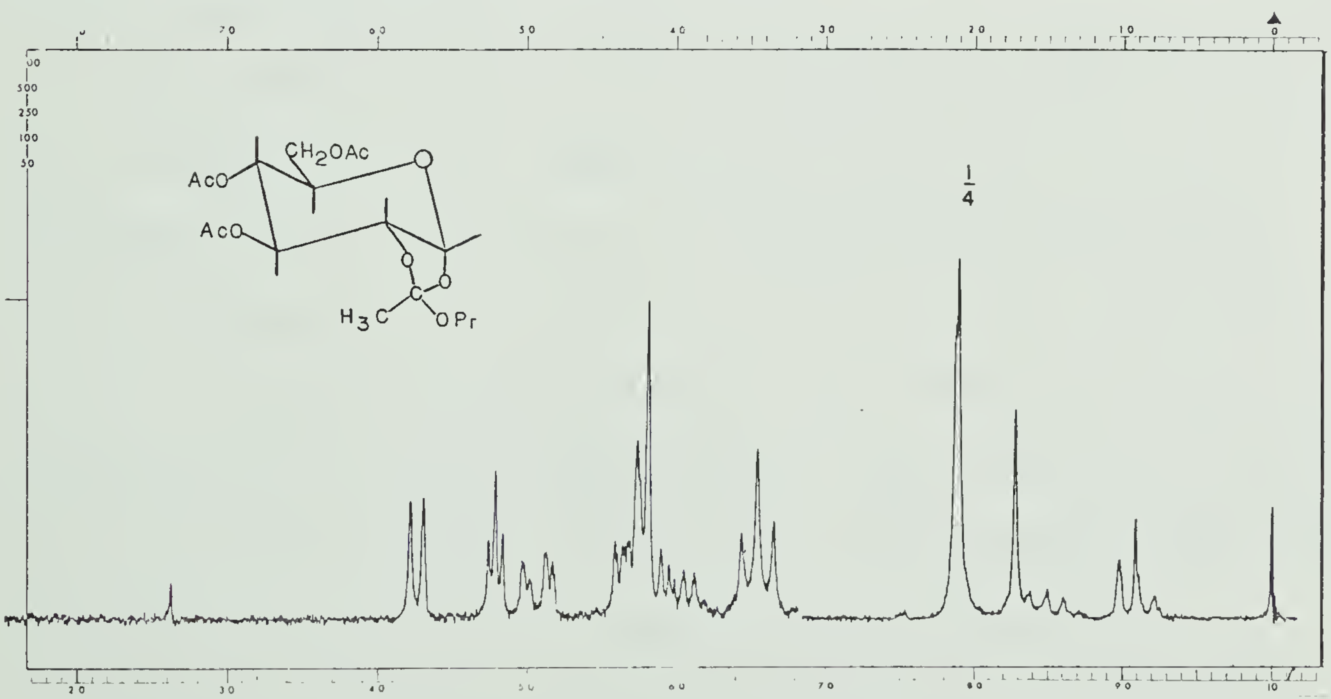


Fig. 24. N.m.r. spectrum (60 MHz) of tri-O-acetyl-1,2-O-(1'-exo-n-propyloxyethylidene)-α-D-glucopyranose (XXIX).

yields of these reactions are given in Table III. A correction of the literature is made in the case of tri-O-acetyl-1,2-O-(1'-exo-n-propyloxyethylidene)-α-D-glucopyranose (XXIX). This compound apparently had been obtained crude by Lemieux and Cipera (18), m.p. 60-69°; two recrystallizations from ethanol yielded a pure compound, m.p. 92-94.5°, $[\alpha]_D$ + 39.5° (c, 1 in chloroform) which was thought to be the n-propyl orthoester. However, an exchange (26) must have taken place to yield the ethyl orthoester (I) which has almost exactly these physical properties. We observed a melting point of 68-69° and an optical rotation $[\alpha]_D^{25}$ + 29°(c, 1 in chloroform) for the pure n-propyl orthoester (XXIX) with the n.m.r. spectrum shown in Fig. 24.

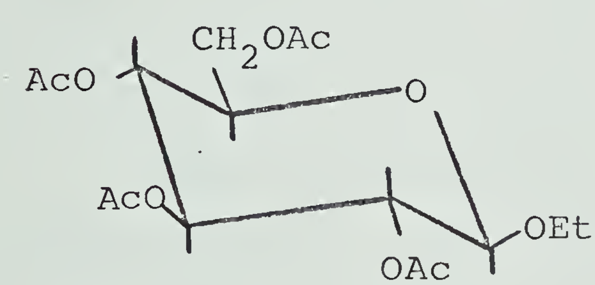
It seemed useful to first discuss the reaction of tri-O-acetyl-1,2-O-(1'-exo-ethoxyethylidene)-α-D-glucopyranose (I) with ethanol and antimony pentachloride. It was found that the ratio of the α- to the β-D-glucosides obtained in this reaction is a function of the concentration of the added alcohol and the catalyst and of the reaction time. Good yields of α-D-glucosides were obtained if one mole of acid was used per mole of orthoester. When the reaction products were separated by silicic acid column chromatography it was found that

ethyl 3,4,6-tri-O-acetyl-α-D-glucopyranoside (XXVIII) and ethyl tetra-O-acetyl-α-D-glucopyranoside (XXVI) were present in a ratio of ∿4:1. XXVI was obtained as a crystalline product and compared with authentic material. The structure of XXVIII was established by n.m.r. spectroscopy. The free hydroxyl group is located at C-2 which was verified by nuclear magnetic double resonance. Irradiation at the resonance frequency of H-1 (τ5.05) altered a multiplet centered at τ6.3, characteristic for a proton attached to a carbon atom bearing a hydroxyl group. Also, irradiation at τ6.3 collapsed the triplet for H-3 at τ4.75 and the doublet for H-1 at τ5.05. It is of interest to note that the methylene protons of the ethoxy group are nonequivalent, which was shown by irradiating at the resonance frequency of the CH_3 protons at τ8.72. Although small amounts of β-D-glucosides were indicated by g. l.c. it was not possible to detect these compounds in the n.m.r. spectra.

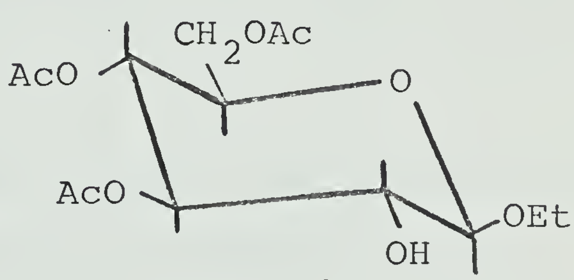
In view of the mechanism of the reaction (discussed later) it is difficult to explain the presence of ethyl tetra-O-acetyl-α-D-glucopyranoside (XXVI) other than by the isomerization of the first formed β-isomer (XXV). We therefore studied the isomerization of both ethyl tetra-O-acetyl-β-D-glucopyranoside (XXV) and ethyl 3,4,6-tri-O-

acetyl-β-D-glucopyranoside (XXVII) and found that almost complete isomerization to the α-anomer takes place under the conditions employed in the above reaction. Similar results have been obtained with boron trifluoride and titanium tetrachloride (91-96). That an axial alkoxy group at the anomeric carbon should be thermodynamically favoured has been termed the anomeric effect (97-102).

It seemed therefore interesting to study the formation of D-glucosides under less acidic conditions. When the amount of added antimony pentachloride was decreased to 0.2 mole per mole of orthoester the α- and β-D-glucoside were obtained in about equal amounts. The products were ethyl 3,4,6-tri-O-acetyl-β-D-glucopyranoside (XXVII),

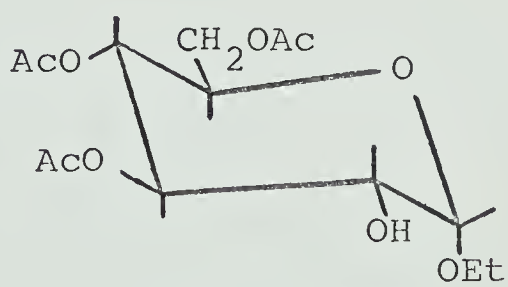


XXVII 24%



XXV 28%

Diagram 23. Products in the formation of ethyl D-glucopyranosides.



XXVIII 48%

ethyl tetra-O-acetyl-β-D-glucopyranoside (XXV) and ethyl 3,4,6-tri-O-acetyl-α-D-glucopyranoside (XXVIII) in a ratio of about 1:1:2 (Diagram 23). The structures of the compounds above were verified by comparison with authentic materials (XXV, XXVIII) or by nuclear magnetic double resonance (XXVII). In the latter case the signal for H-1 at τ5.63 was the only one which was found to be amenable to first order analysis. The spacing of 8 Hz is characteristic for protons in a diaxial relationship, therefore the anomeric configuration is β. Irradiation at τ5.63 altered a multiplet at τ6.35 indicating that H-2 is not deshielded by an acetyl group. The multiplet at τ4.9 was assigned to H-3 and H-4, H-3 being to lower field compared to H-4. Again the methylene protons of the ethoxy group are not equivalent which had been found to be the case for the α-isomer.

When the addition of the alcohol was omitted in the above reaction, the β-D-glucosides predominated in the reaction mixture. In the case where 0.1 mole of antimony pentachloride was used per mole of orthoester the ethyl β-D-glucopyranoside was obtained in 73% yield, as indicated by g. l.c. This result is similar to those obtained by Helferich (20) and Kochetkov (27) who used hydrogen chloride and mercuric chloride. These workers

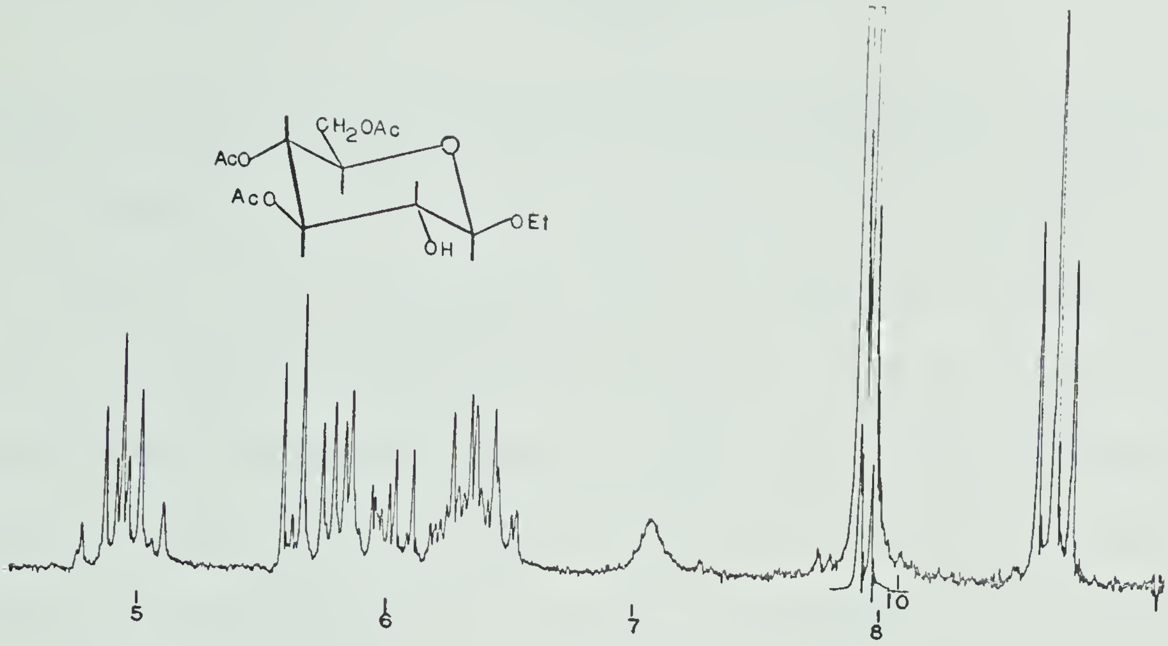


Fig. 25. N.m.r. spectrum (100 MHz) of ethyl 3,4,6-tri-O-acetyl-β-D-glucopyranoside (XXVII) ($CDCl_3$).

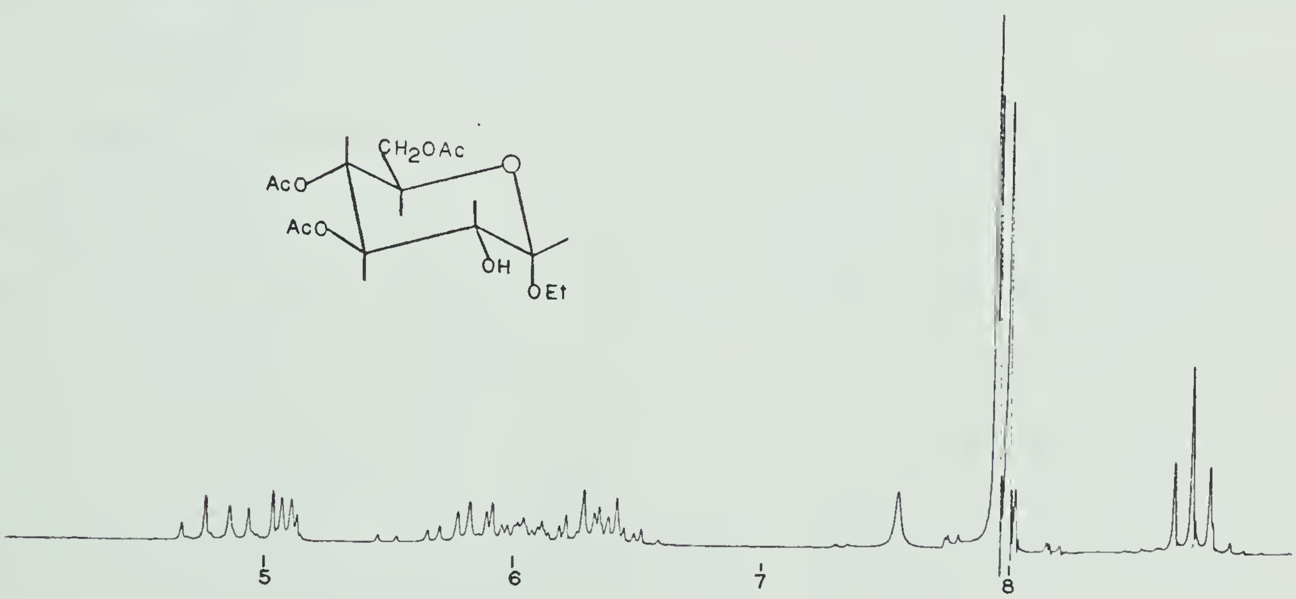


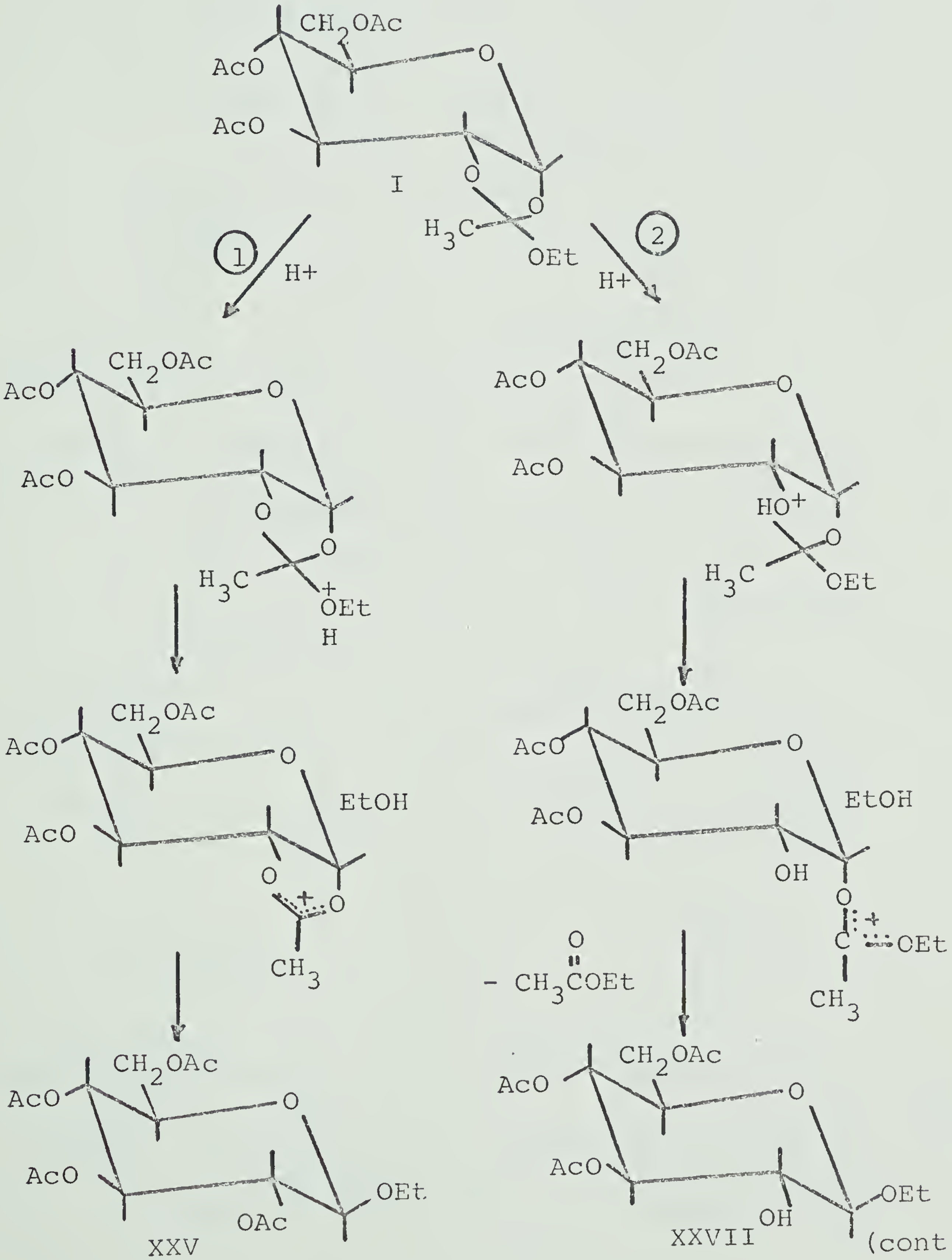
Fig. 26. N.m.r. spectrum (100 MHz) of ethyl 3,4,6-tri-O-acetyl-α-D-glucopyranoside (XXVIII)($CDCl_3$).

isolated alkyl tetra-O-acetyl-β-D-glucopyranosides as the major products. It is of interest to note that Montgomery and Franks (103) obtained similar results in the D-mannose series. The reaction of tri-O-benzyl-1,2-O-(1'-methoxy-ethylidene)-β-D-mannopyranose with p-toluenesulfonic acid yielded methyl 2-O-acetyl-tri-O-benzyl-α-D-mannopyranoside indicating trans-opening of the orthoester. The addition of methanol resulted in a more extensive loss of the 2-acetoxy group which is similar to our results.

In view of the different products obtained under various conditions it seems that more than one mechanism can be envisaged for the reaction of an alkyl 1,2-ortho-ester with an alcohol and an acidic catalyst (Diagram 24).

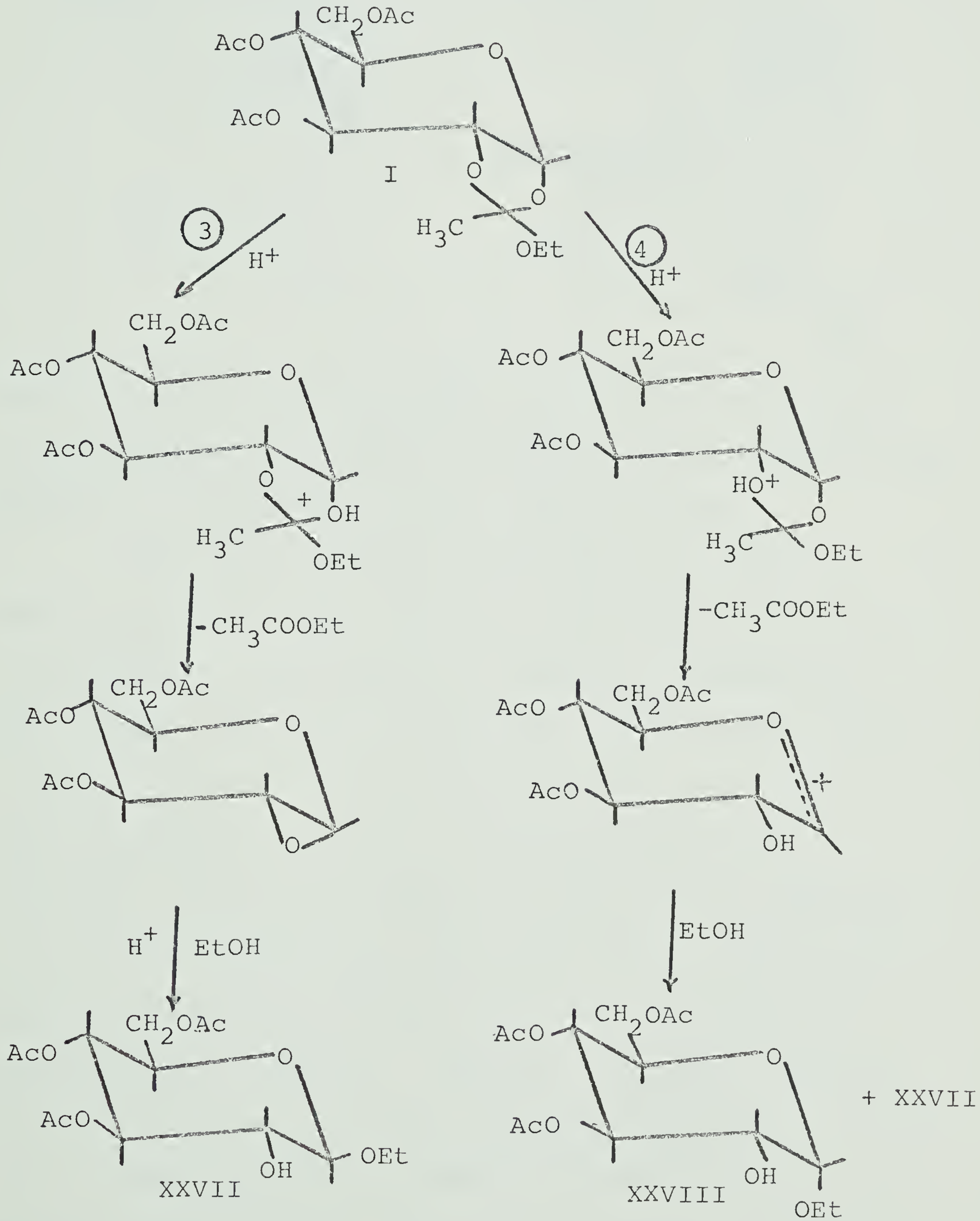
Formation of the acetoxonium ion (Route 1) and nucleophilic attack of the alcohol to give trans opening, produces ethyl tetra-O-acetyl-β-D-glucopyranoside (XXV). This seems to be the only possible route if the addition of an alcohol is omitted, since 2, 3 and 4 would result in the loss of ethyl acetate. The presence of ethyl-tetra-O-acetyl-α-D-glucopyranoside (XXVI) can only be explained by isomerization of the β-isomer, unless the possibility of a rearrangement (Diagram 25) is taken into account. Lemieux and Morgan (8) ruled out such a rearrange-ment on the basis of their results. Route 1 (formation of

Diag. 24. Mechanistic investigations in the formation of D-glucopyranosides.



(cont'd.)

Diag. 24 (Cont'd.)



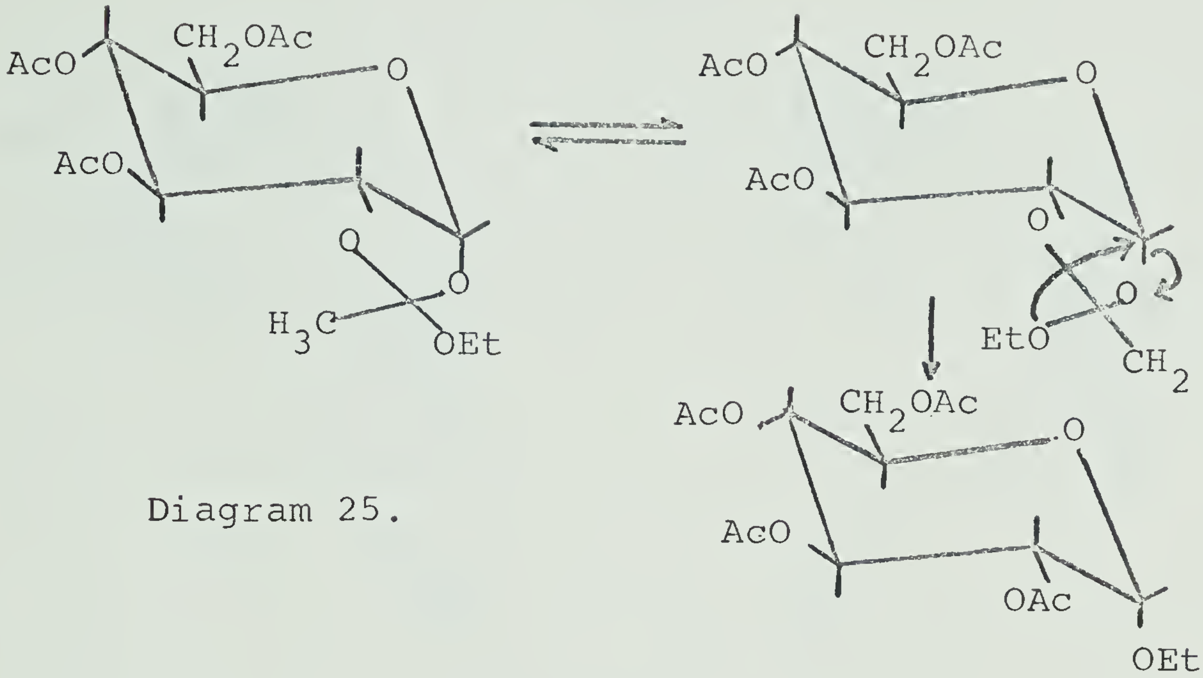
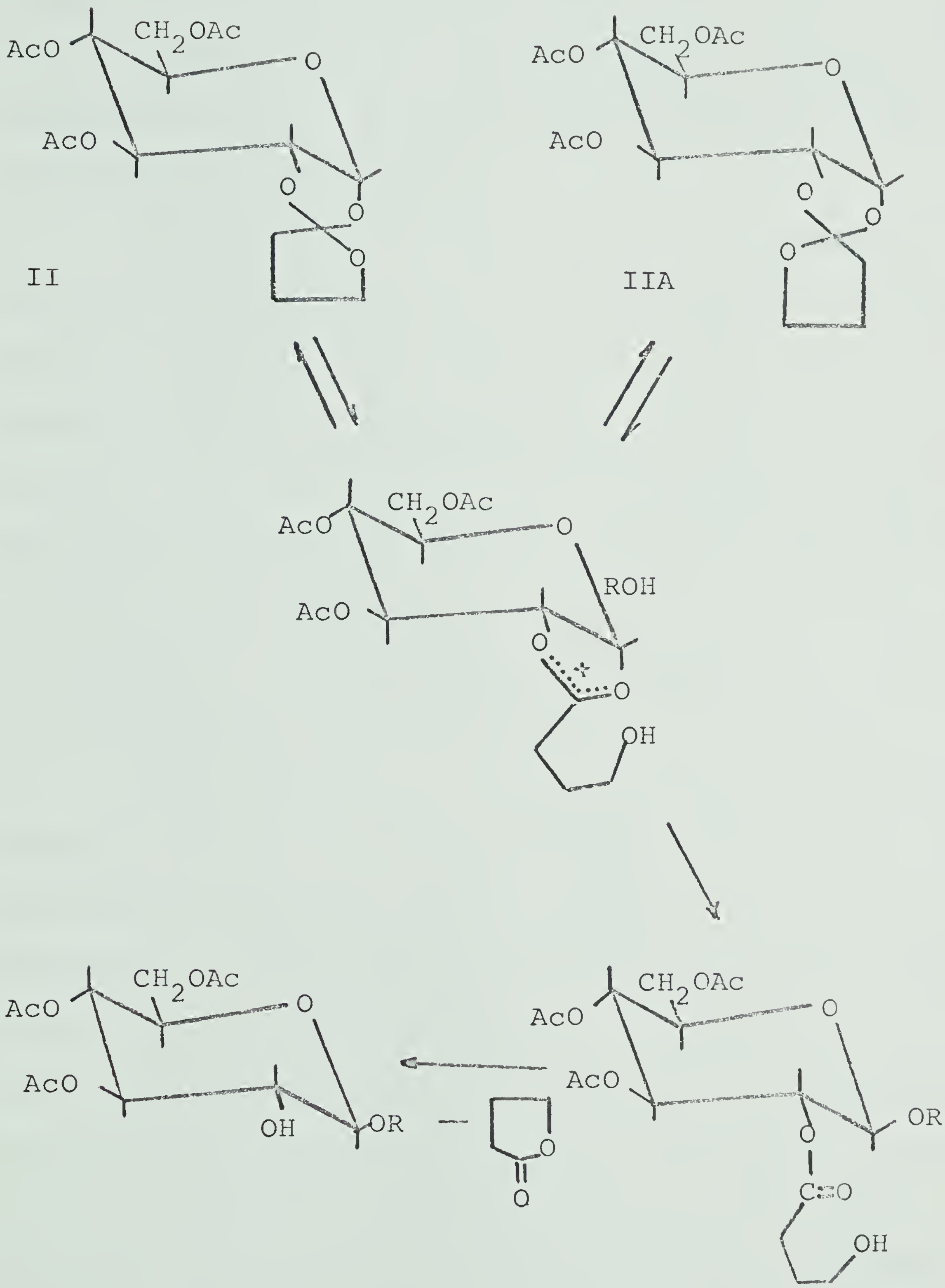


Diagram 25.

the acetoxonium ion) also would explain that n-propyl D-glucopyranosides were formed (∿30%) in the reaction of the n-propyl 1,2-orthoester (XXIX) with 2-propanol.

The cyclic carbonium ion (route 4), which is stabilized by the ring oxygen, has been postulated as an intermediate in the reaction of alkyl 1,2-orthoesters with alcohols and p-toluenesulfonic acid (8) and also in the anomerization of β-D-glucosides (96). In these reactions the major product was found to be the α-D-glucoside. Since the formation of the cyclic carbonium ion involves the loss of ethyl acetate this route would explain the presence of ethyl 3,4,6-tri-O-acetyl-α-D-glucopyranoside (XXVIII). However, the latter compound can also arise by way of the isomerization of the β-isomer.

The occurrence of ethyl 3,4,6-tri-O-acetyl-β-D-glucopyranoside (XXVII) can be seen to have arisen from



Diag. 26. Formation of D-glucopyranosides from spiro orthoesters II, IIA.

routes 2 and 3. Lemieux and Morgan (8) showed that the acid catalyzed reaction of tri-O-acetyl-1,2-anhydro-α-D-glucopyranose with an alcohol resulted mainly in the formation of β-D-glucosides.

In the reaction of the epimeric tri-O-acetyl-1,2-O-(2'-oxacyclopentylidene)-α-D-glucopyranoses (II, IIA) with an alcohol and antimony pentachloride similar reaction paths can be postulated. In this case the anomeric alkyl 3,4,6-tri-O-acetyl-D-glucopyranosides were the products and according to the reaction conditions varying ratios of these two compounds were obtained. As is expected 4-butyrolactone was formed. The presence of this compound was detected by g. l.c. and n.m.r.

As was the case for the alkyl 1,2-orthoesters routes 2 and 3 would explain the formation of the β-D-glucoside, whereas the cyclic carbonium ion 4 would produce mainly the α-D-glucoside. The possibility of protonation of the oxygen atom in the oxacyclopentylidene ring (Diagram 26), analogously to route 1 in Diagram 24, and subsequent ring opening can not be excluded. Nucleophilic attack of the alcohol to open the oxonium ion would yield a compound which bears the highly acid labile 4-hydroxy-butyryl group at C-2. Lactonization of this group would result in the formation of the alkyl 3,4,6-tri-O-acetyl-

β-D-glucopyranoside and 4-butyrolactone.

The reaction of tri-O-acetyl-1,2-O-cyclopentylidene-α-D-glucopyranose (XXXVI) with antimony pentachloride and 2-propanol gave virtually the same results as the 1,2-orthoesters (Table III). Routes 2, 3 and 4 (Diagram 24) can be envisaged as possible reaction paths in the formation of isopropyl D-glucosides.

To date Lemieux and Morgan's (7) synthesis of 1,2-orthoesters was applied only to D-glucose. It was considered of interest to extend their method to the D-galactose series.

Reaction of tetra-O-acetyl-α-D-galactopyranosyl bromide with methanol, ethanol (104) and benzyl alcohol, using 2,6-lutidine as solvent and tetra-n-butylammonium bromide as catalyst, provided near quantitative yields of the respective 1,2-orthoesters. The ratios of the <u>exo</u> to <u>endo</u> isomers were calculated from the n.m.r. spectra of the crude reaction products and are shown in Table I. As was the case in the D-glucose series the <u>exo</u> isomer was formed as the major component. Lemieux and Cipera (18) suggested that the high degree of stereoselectivity (over 85% <u>exo</u>) arises because of easier approach by the alcohol to the side of the 1,2-acetoxonium ion which is <u>trans</u> to the glucopyranose ring, the other side being

sterically hindered (Diagram 27). In the D-galactose series this hindrance seems to occur to a slightly lesser extent which can probably be explained by the absence of an equatorial acetoxy group at C-4. In the case of the methyl and the ethyl 1,2-orthoester the ratio of the <u>exo</u> to <u>endo</u> isomer was found to be about 70:30 whereas for the bigger molecule of benzyl alcohol a ratio of about 90:10 was observed. The n.m.r. parameters for the

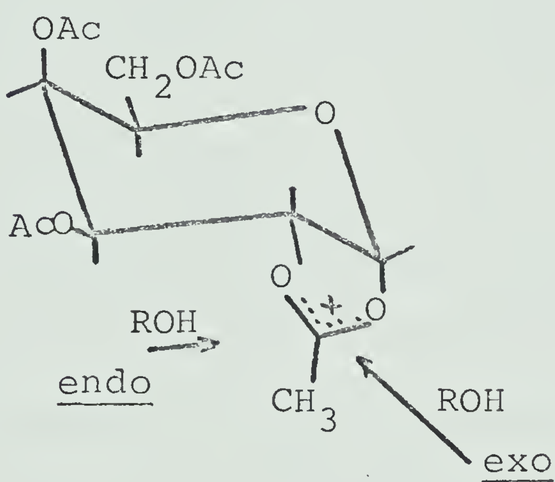


Diagram 27.

<u>exo</u> D-galactose 1,2-orthoesters are presented in Table XI. It can be seen that a change in the bulk of the alkoxy group in these compounds does not have any effect on the coupling constants. The magnitude of the coupling constants indicates that the pyranose ring is slightly distorted, assuming the conformation of a flattened chair, analogously

to the observation in the D-glucose series. The dihedral angles calculated for the D-galactose 1,2-orthoesters are shown in Table VIII. Although the signals for the anomeric protons of the <u>endo</u> isomers could be readily detected at $\tau \sim 4.35$, it was not possible to observe the signals for the other ring protons.

Hydrolysis of tri-O-acetyl-1,2-O-(1'-ethoxy-ethylidene)-α-D-galactopyranose (XLIII) with 95% aqueous acetic acid as well as hydrogenolysis of tri-O-acetyl-1,2-O-(1'-benzyloxyethylidene)-α-D-galactopyranose (XLIV) yielded 1,3,4,6-tetra-O-acetyl-α-D-galactopyranose (XLV) as a crystalline product (Diag. 28). Helferich and Zirner (68) prepared this compound by hydrolysis of tetra-O-acetyl-α-D-galactopyranosyl bromide, analogously to the procedure used for the preparation of 1,3,4,6-tetra-O-acetyl-α-D-glucopyranose (IX). Earlier Helferich and Steinpreis (105) thought that the product was in fact 2,3,4,6-tetra-O-acetyl-α-D-galactopyranose.

The n.m.r. spectrum of the material obtained by us, with the same physical properties as that of Helferich (68, 104) is shown in Fig. 30. The structure indicated by the spectrum is clearly that of 1,3,4,6-tetra-O-acetyl-α-D-galactopyranose (XLV). The anomeric configuration is α which is shown by the spacing of 3.8 Hz

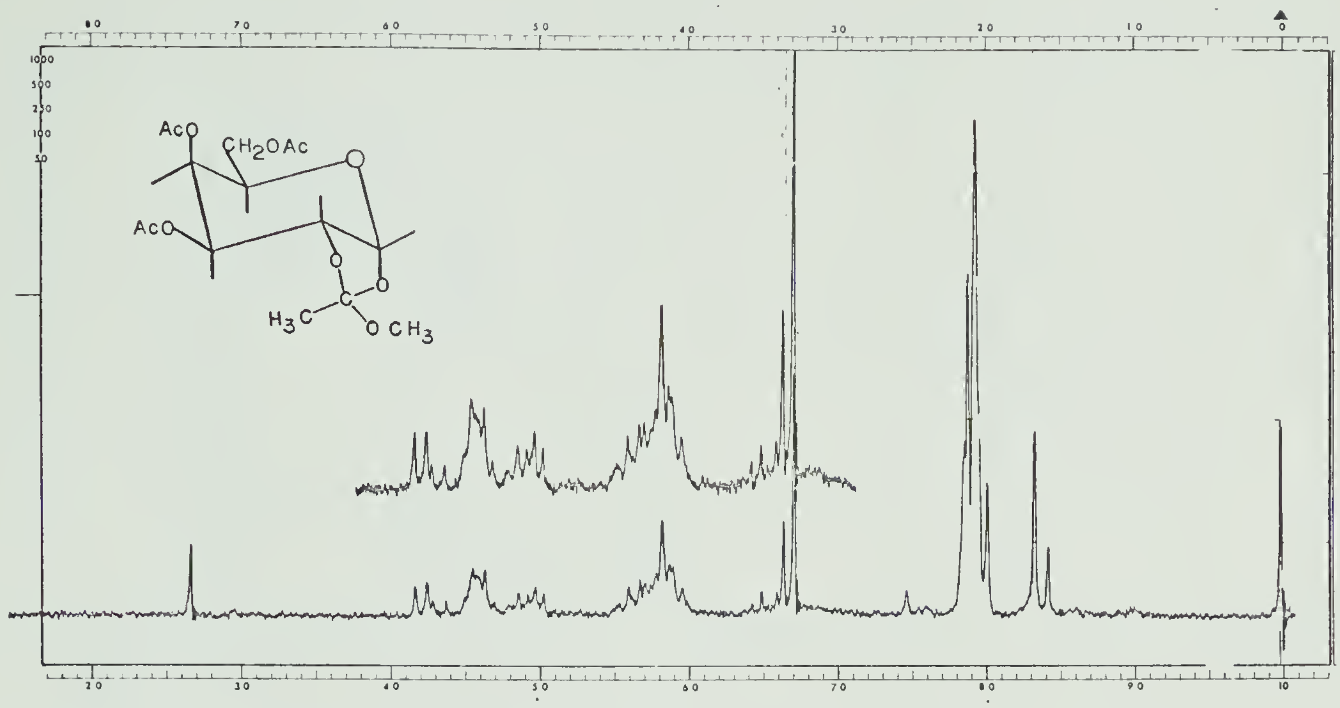


Fig. 27. N.m.r. spectrum (60 MHz) of tri-O-acetyl-1,2-O-(1'-methoxyethylidene)-α-D-galactopyranose (XLII) ($CDCl_3$).

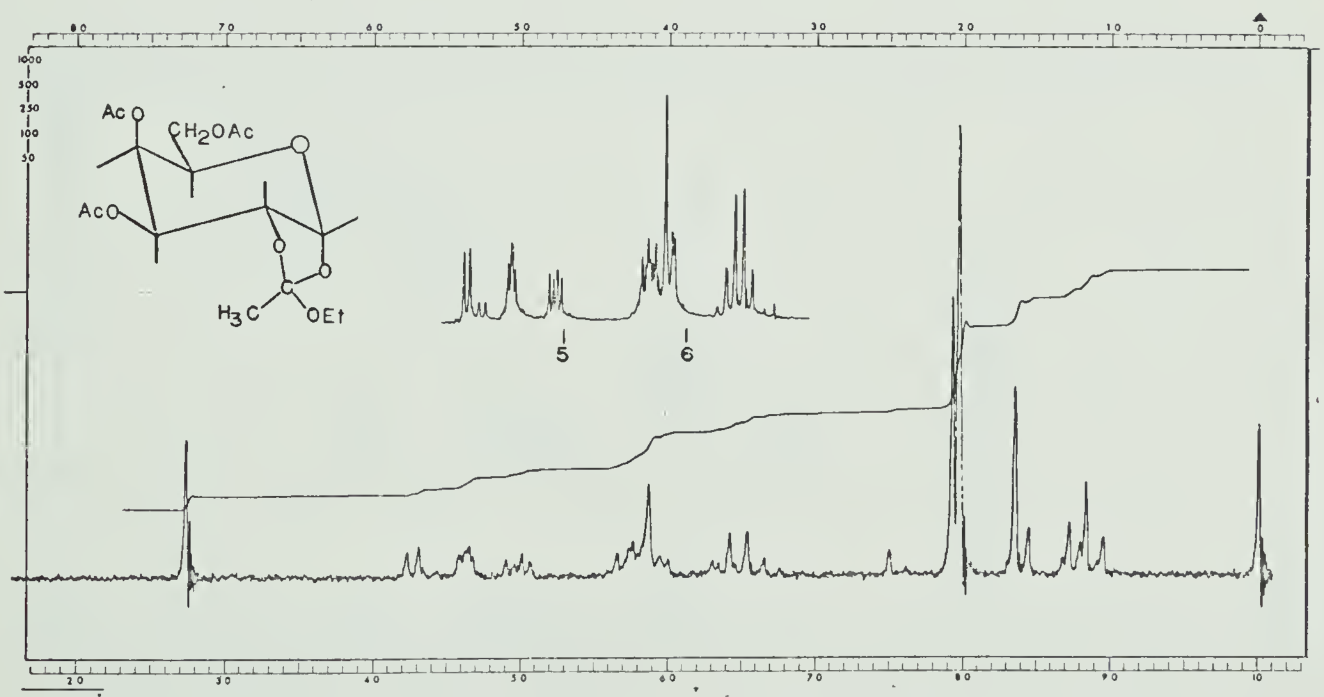


Fig. 28. N.m.r. spectrum (60 MHz) of tri-O-acetyl-1,2-O-(1'-ethoxyethylidene)-α-D-galactopyranose (XLIII) ($CDCl_3$). Inset (100 MHz) ($CDCl_3$).

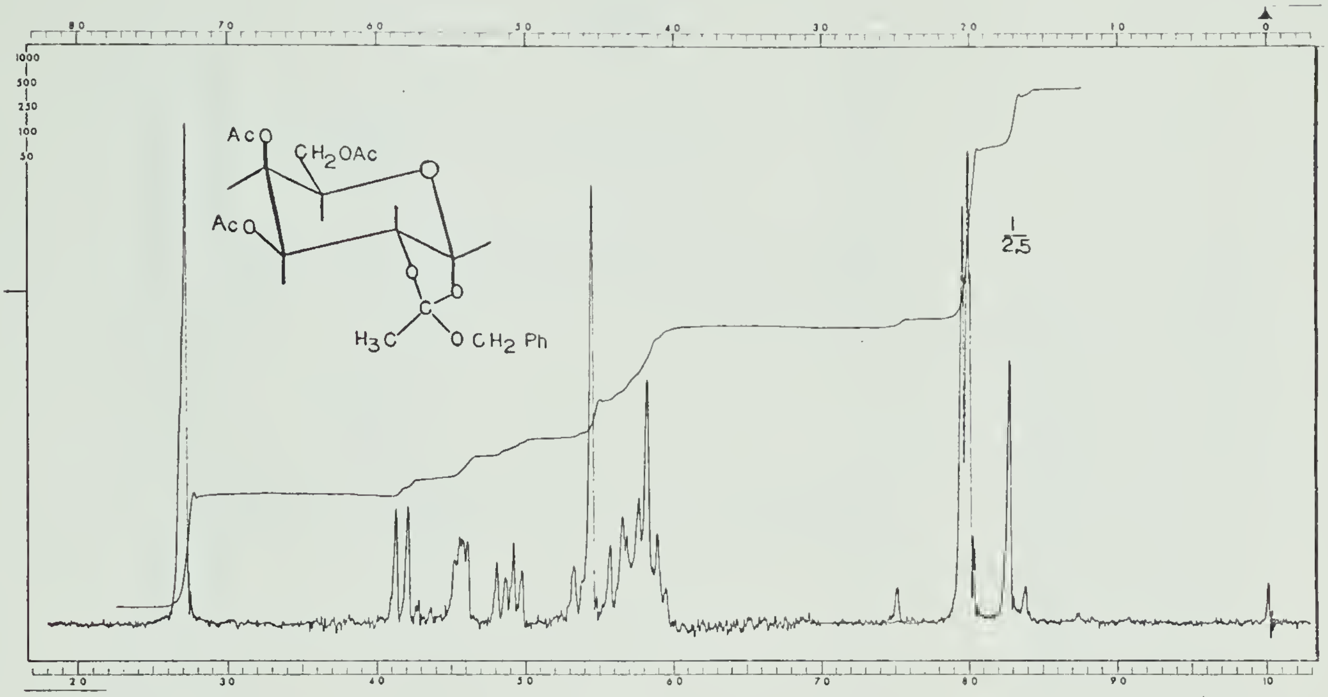


Fig. 29. N.m.r. spectrum (60 MHz) of tri-O-acetyl-1,2-O-(1'-benzyloxyethylidene)-α-D-galactopyranose (XLIV) ($CDCl_3$).

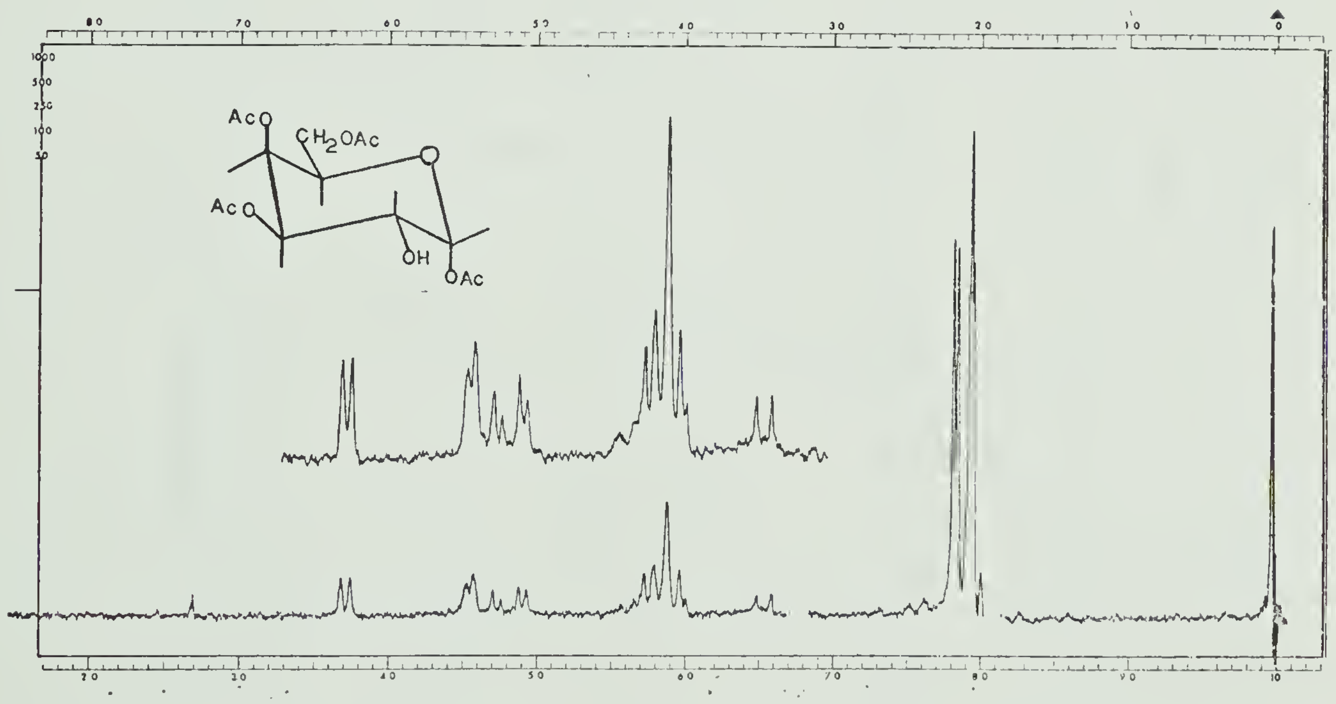


Fig. 30. N.m.r. spectrum (60 MHz) of 1,3,4,6-tetra-O-acetyl-α-D-galactopyranose (XLV) ($CDCl_3$).

Table XI. N.m.r. parameters (60 MHz, $CDCl_3$) of 1,2-orthoesters of D-galactopyranose.

exo Isomer	H-1 (τ)	$J_{1,2}$ (Hz)	H-3 (τ)	$J_{2,3}$ (Hz)	H-4 (τ)	$J_{3,4}$ (Hz)	$J_{4,5}$ (Hz)
XLII	4.20[a]	5.0	4.94	6.5	4.58	3.5	2.5
XLIII	4.17[b]	5.0	4.89	6.5	4.54	3.5	2.5
XLIV	4.16[c]	5.0	4.87	6.5	4.56	3.5	2.5

endo Isomer: _a_. 4.29, _b_. 4.31, _c_. 4.32.

XLII: Tri-0-acetyl-1,2-0-(1'-_exo_-methoxyethylidene)-α-D-galactopyranose.

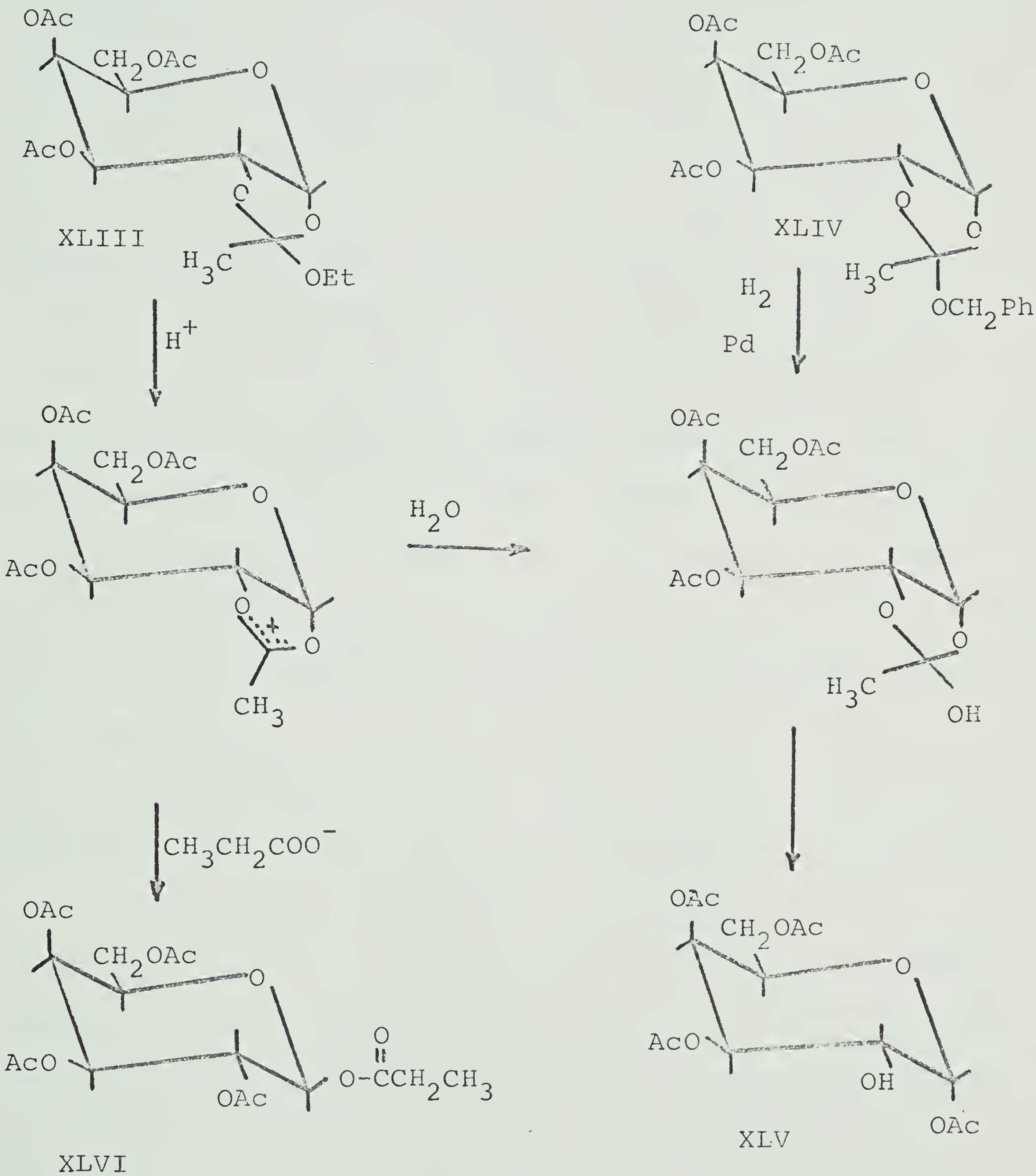
XLIII. Tri-0-acetyl-1,2-0-(1'-_exo_-ethoxyethylidene)-α-D-galactopyranose.

XLIV. Tri-0-acetyl-1,2-0-(1'-_exo_-benzyloxyethylidene)-α-D-galactopyranose.

for the doublet at τ3.67, characteristic for a gauche pair of protons. The two signals shifted downfield to τ7.82 and τ7.85, compared to equatorial acetoxy groups, are typical for axial acetoxy groups. The signal for the equatorial H-4 is shifted downfield by ∿0.5 ppm compared to the axial H-4 in 1,3,4,6-tetra-O-acetyl-α-D-glucopyranose (IX). The doublet with spacing of 6.5 Hz at τ6.55 was assigned to the hydroxyl proton. This signal had disappeared after the chloroform solution had been shaken with D_2O. Examination of the compound (XLV) in DMSO-d_6 solution at 100 MHz verified the above assignments and provided the coupling constants listed in Table IV; the signals of H-3 and H-4 were now amenable to first order analysis. The signal for the proton at C-2 is shifted to high field compared to H-3 and H-4, which is due to the absence of a deshielding acetoxy group (106).

Reaction of tri-O-acetyl-1,2-O-(1'-ethoxyethylidene)-α-D-galactopyranose (XLIII) with dry propionic acid yielded tetra-O-acetyl-1-O-propionyl-β-D-galactopyranose (XLVI). Although the syrup could not be induced to crystallize, the n.m.r. spectrum could be interpreted as that of XLVI and could be readily compared with that of penta-O-acetyl-β-D-galactopyranose.

It was considered of interest to extend the



Diag. 28. Solvolysis reactions of 1,2-orthoesters of D-galactopyranose.

solvolysis reactions, studied in the case of D-glucose and D-galactose, to the D-mannose series. Previously Perlin (24) reacted <u>exo</u> and <u>endo</u> 1,2-O-(1'-benzyloxyethylidene)-β-D-mannopyranose with aqueous hydrochloric acid and obtained 2-O-acetyl-D-mannose as the major product in both cases. When we dissolved tri-O-acetyl-1,2-O-(1'-<u>exo</u>-methoxyethylidene)-β-D-mannopyranose (IV) in 95% aqueous acetic acid, two crystalline compounds 2,3,4,6-tetra-O-acetyl-α-D-mannopyranose (XLVIII) and 1,3,4,6-tetra-O-acetyl-β-D-mannopyranose (XLVII), were isolated in a ratio of about 1:1. The n.m.r. spectrum of the crude reaction mixture, however, indicated a ratio of about 60:40 for the 2,3,4,6-tetraacetate and the 1,3,4,6-tetraacetate. It seemed safe to conclude that some 2,3,4,6-tetra-O-acetyl-β-D-mannopyranose (LII) was present in the mixture, although this compound could not be identified positively.

The results obtained are in accord with the findings of Bonner (69) who obtained the three mentioned isomers of tetra-O-acetyl-D-mannopyranose in the reaction of tetra-O-acetyl-α-D-mannopyranosyl chloride and bromide with silver carbonate and water. The mechanism for the formation of the three compounds can be depicted as seen in Diagram 29. A resonance stabilized acetoxonium ion

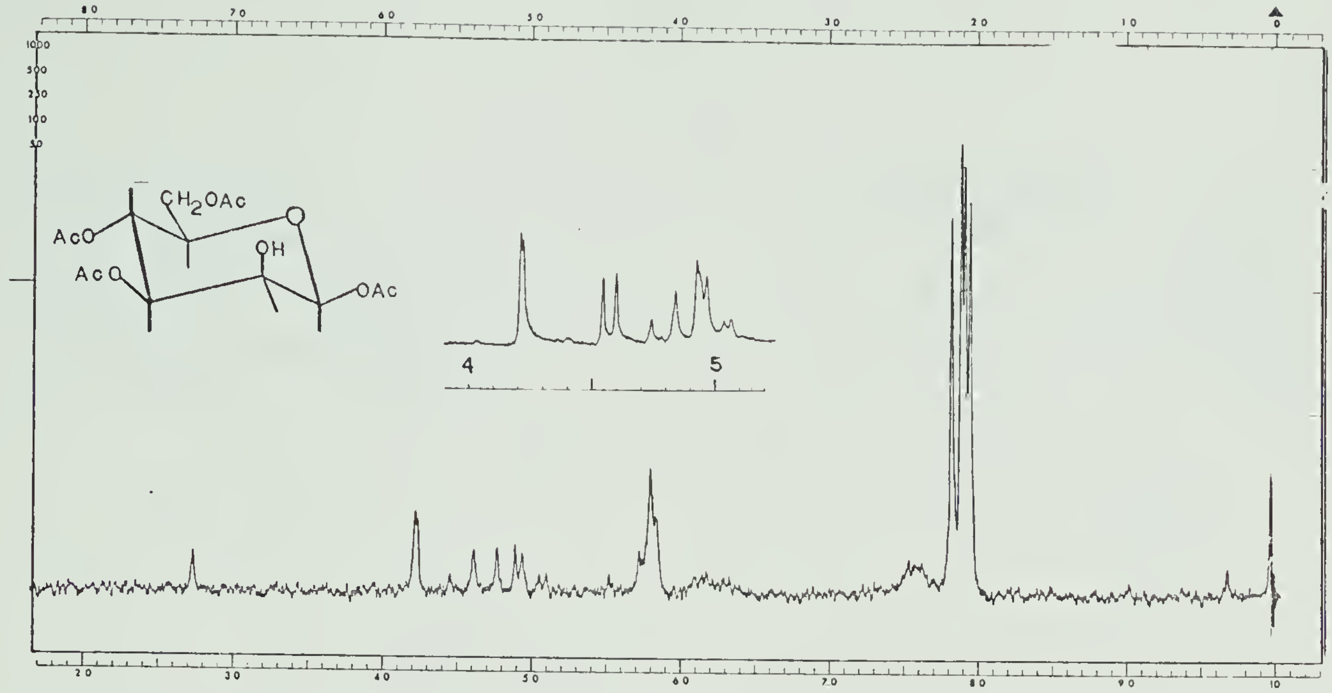


Fig. 31. N.m.r. spectrum (60 MHz) of 1,3,4,6-tetra-O-acetyl-β-D-mannopyranose (XLVII) ($CDCl_3$). Inset (100 MHz) (DMSO-d_6).

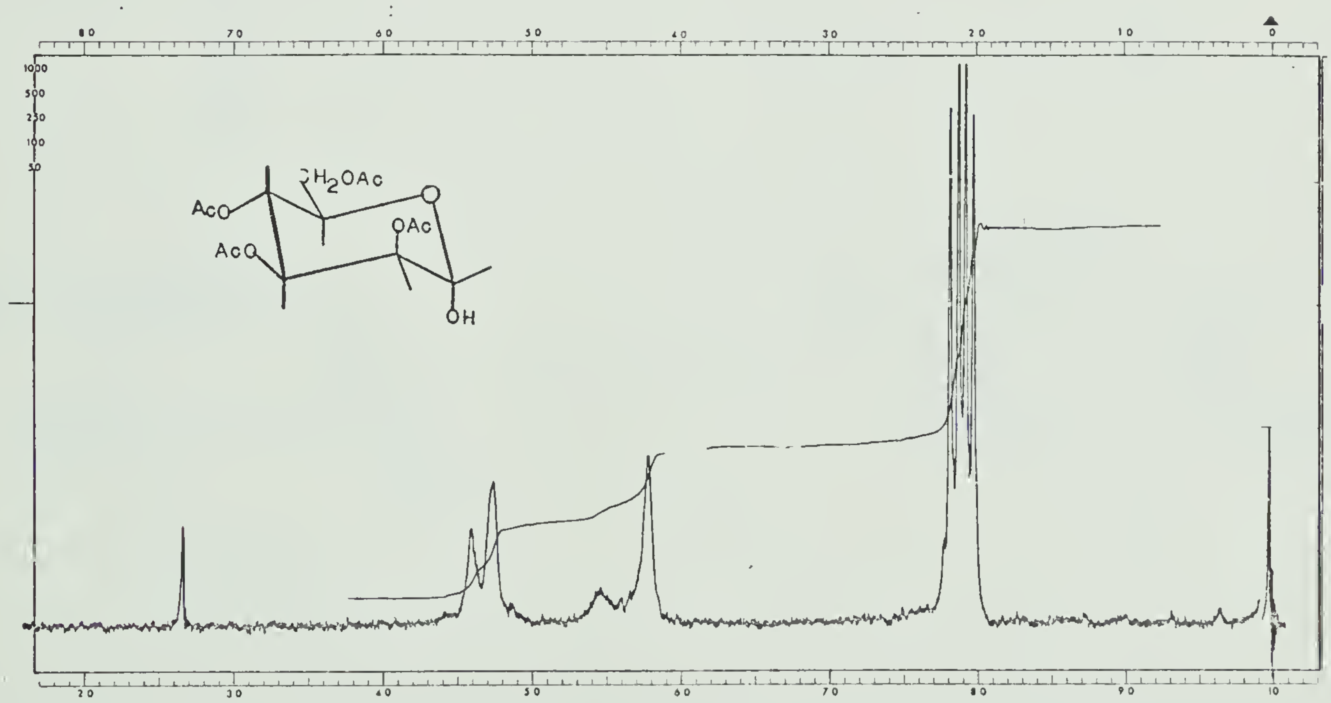
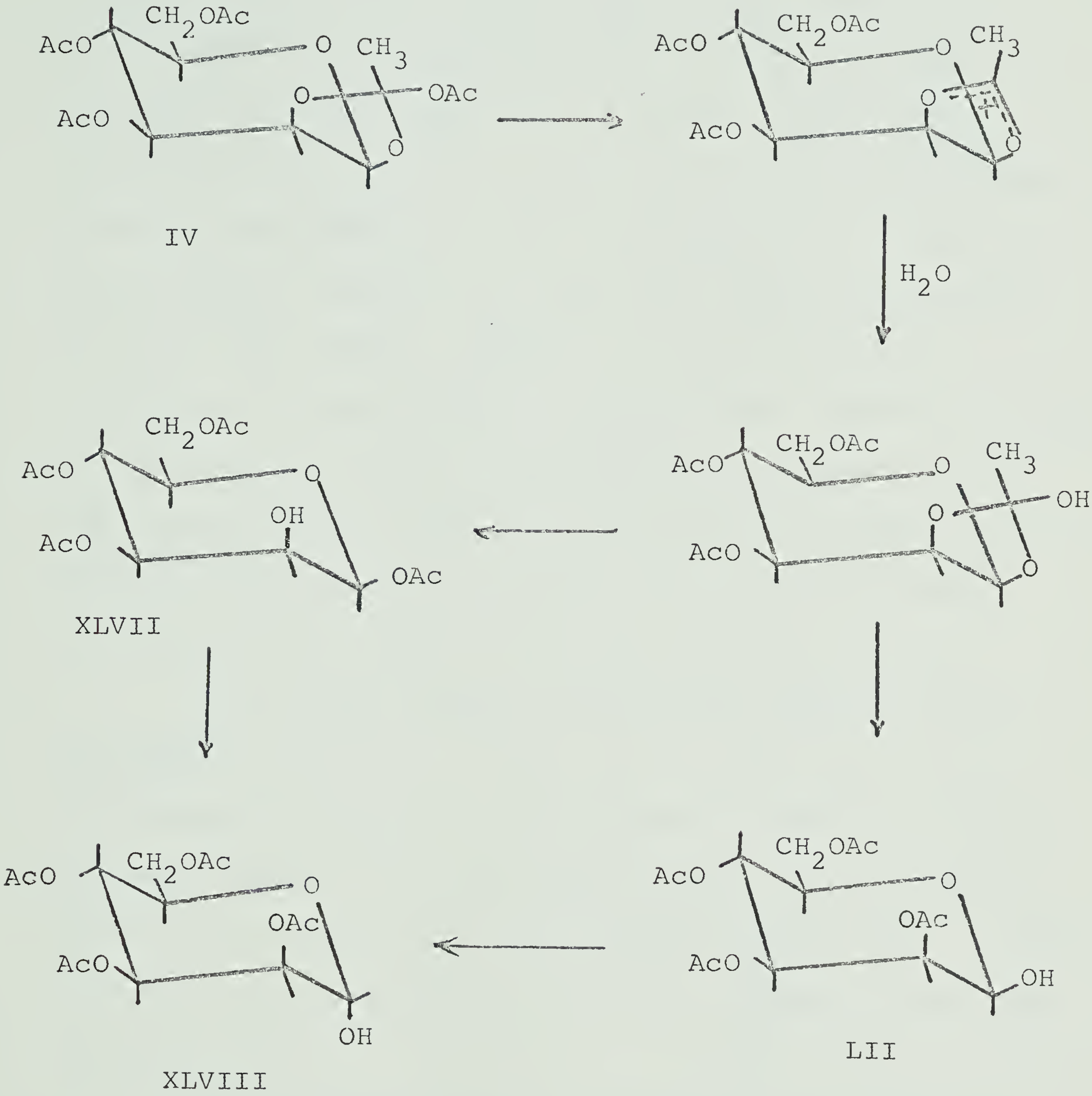


Fig. 32. N.m.r. spectrum (60 MHz) of 2,3,4,6-tetra-O-acetyl-α-D-mannopyranose (XLVIII) ($CDCl_3$).

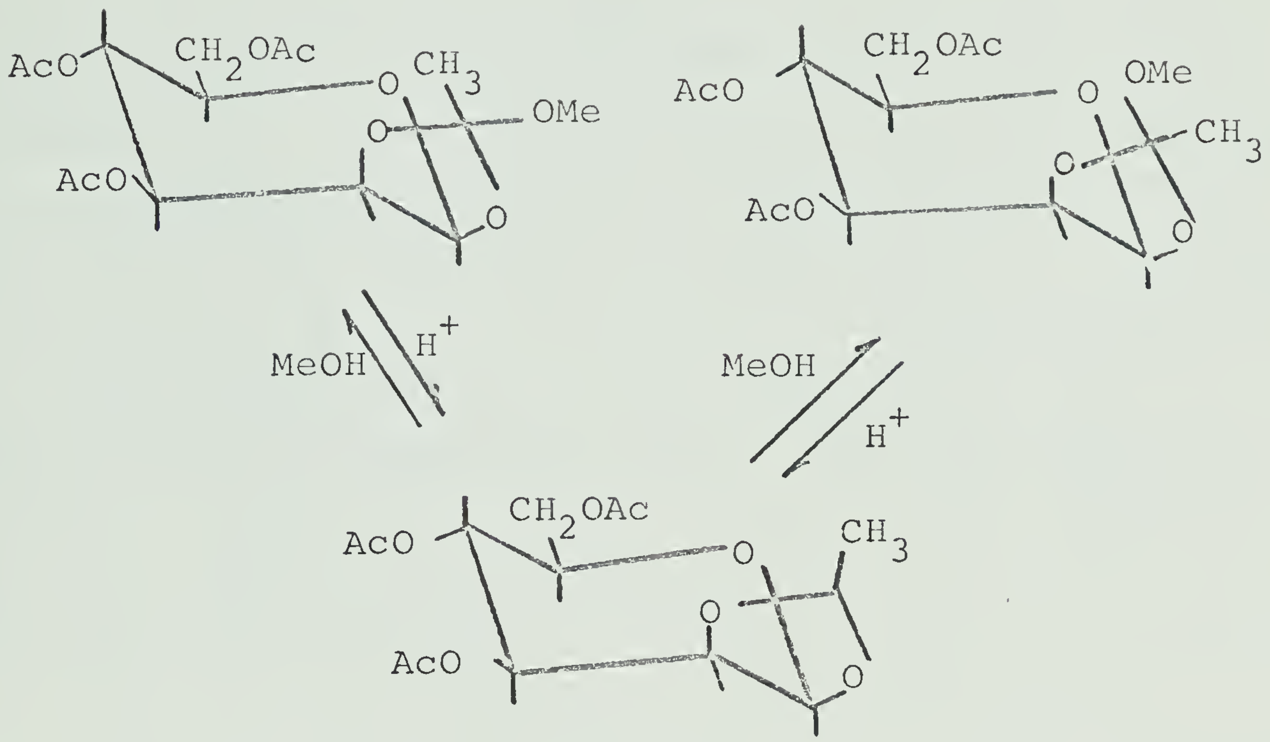


Diag. 29. Solvolysis reactions of 1,2-orthoesters of D-mannopyranose.

is formulated, which reacts with the water present to form the transient orthoacid which in turn can then collapse to yield either LII or XLVII. Bonner (69) studied the mutarotation of all three isomers in aqueous solution and found that XLVII isomerized very slowly to yield XLVIII, whereas LII anomerized comparatively fast to yield also XLVIII. Since in our experiments no attention was paid to the use of strictly anhydrous solvents in the recrystallization procedures, the absence of LII can be explained. When the isomerization of XLVII in 95% aqueous acetic acid was studied over a 1/2 hour period no change of the optical rotation could be detected.

The 60 MHz spectra of the pure compounds XLVII and XLVIII are shown in Figs. 31, 32. The signal for the anomeric proton in 1,3,4,6-tetra-O-acetyl-β-D-manno-pyranose (XLVIII) at τ4.19 with spacing 1 Hz is typical for a β-1-O- acetate in the D-mannose series (106). Penta-O-acetyl-β-D-mannopyranose exhibits a doublet of spacing 1 Hz at τ4.10.

It was found that the reaction of tri-O-acetyl-1,2-O-(1'-exo-methoxyethylidene)-β-D-mannopyranose (IV) with dry propionic acid was very slow compared to the analogous reactions in the D-glucose and D-galactose series. After 24 hours at room temperature only



Diag. 30. Diastereoisomeric tri-O-acetyl-1,2-O-(1'-methoxyethylidene)-β-D-mannopyranoses.

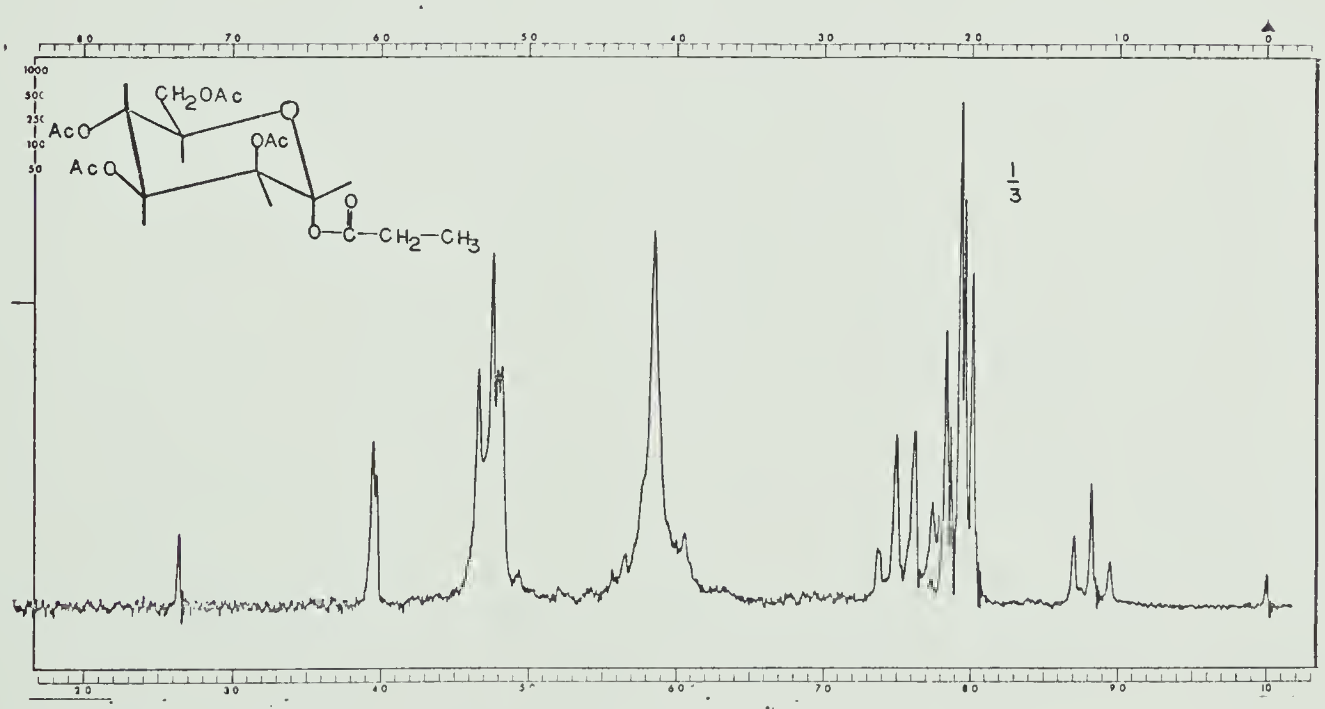


Fig. 33. N.m.r. spectrum (60 MHz) of tetra-O-acetyl-1-O-propionyl-α-D-mannopyranose (LI) ($CDCl_3$).

isomerization of the starting material had taken place (Diagram 30). At an elevated temperature of 50°, however, tetra-O-acetyl-1-O-propionyl-α-D-mannopyranose (LI) was obtained in near quantitative yield. The n.m.r. spectrum of this compound can be readily compared with that of penta-O-acetyl-α-D-mannopyranose. Both these compounds exhibit a doublet of spacing 1.5 Hz at τ3.95, representing the anomeric protons.

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